Outcomes of Colorectal Cancer treatment in daily practice, a descriptive study

van Eeghen, E.E.

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OUTCOMES OF COLORECTAL CANCER TREATMENT IN DAILY PRACTICE, A DESCRIPTIVE STUDY

Elmer van Eeghen

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OUTCOMES OF COLORECTAL CANCER TREATMENT IN DAILY PRACTICE, A DESCRIPTIVE STUDY

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door

Elmer Ernst van Eeghen
geboren te Amsterdam

promotor: prof.dr. C.J.J. Mulder

copromotor: dr. R.J.L.F. Loffeld

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ABSTRACT

Colorectal cancer is increasingly diagnosed in elderly patients. Sixty-seven percent of cases occurs in patients over 65, and 17% in patients over 80 years of age. This review will summarize the available literature and provide a risk/benefit analysis for the major curative treatment options for colon cancer to enable clinicians to develop individualized treatment plans for their elderly patients.

Colon cancer surgery in patients over 75 years of age has a thirty-day mortality rate of 3 – 16%. One-year survival is 78-82%. Patients who do not undergo surgery, have both a higher cancer-specific and all-cause mortality rate. Of patients who do not undergo surgery, 10% requires treatment for acute bowel obstruction later. Emergency surgery is associated with increased mortality and morbidity and should be prevented when possible. Laparoscopic surgery is superior to open procedures when comparing perioperative complications and hospital stay.

Adjuvant chemotherapy increases recurrence-free and overall survival in a selected population. It is unclear whether patients who are currently deemed unfit for treatment would benefit. In patients treated with adjuvant chemotherapy adverse events do not increase with age.

INTRODUCTION

Colorectal cancer is increasingly diagnosed in elderly patients with an incidence of 15.427 in the Netherlands in 2016. Over 67% of cases occurred in patients over 65, and 17% in patients over 80 years of age. [1] In the last 20 years, the treatment options for colorectal cancer have expanded dramatically. There are new surgical techniques, as well as new chemotherapeutic options such as oxaliplatin and targeted therapy with panitumumab and bevacizumab, resulting in increased overall survival. [2] However, these treatments are associated with significant toxicity and peri-procedural risks. Many of the studies demonstrating the effectiveness of these treatments included a young population with little comorbidity that does not adequately represent the average patient in daily practice. [3-5] As such, the benefits in an elderly population more prone to adverse events and with a higher mortality risk from competing causes may be overestimated. Our study shows that of the octogenarians with colorectal cancer and an overall survival of fewer than 5 years 46% died as a result of the tumour. However 22% died due to treatment complications. [6] The challenges in managing frail elderly patients require an individualized approach to curative treatment.

CURATIVE SURGERY FOR COLON CANCER

The percentage of patients undergoing surgery declines with increasing age. Also, the perioperative morbidity and mortality risks increase, which is partly explained by the higher occurrence of emergency surgery in this population. Few randomized clinical trials (RCT's) have been conducted that include elderly patients in this field, and as such any recommendations have to be based on retrospective studies with a considerable bias by indication.

Two large cohort studies by Neuman et al. and Faiz et al. have been performed investigating elderly patients undergoing curative surgery for colon cancer. The study by Neuman also included patients who received conservative treatment. [7,8] Table 1 shows an overview of several studies and their reported post-operative survival. [7-14] The conservatively treated patients were significantly older and more frail. One-year survival was 56% in the conservatively managed group versus 78% in the group undergoing surgery. Colon cancer specific 1-year survival was 78% and 89% respectively. Of the patients who underwent curative resection, only 53% could be performed in an elective setting. The outcome of emergency surgery was significantly worse, with a 1-year survival of 70% versus 86%. Kolfschoten et al. even show 30-day mortality rates of up to 41% in elderly patients with additional risk factors undergoing emergency surgery. [15] Of the patients who received conservative treatment 10.7% required a delayed intervention due to obstruction. The results of the study by Faiz were similar to those reported by Neuman in the surgery group with a 5.4% 30-day mortality rate and 1-year overall survival of 82%. [8] Interestingly, the bulk of mortality does not occur in the immediate post-operative period but in the year after surgery and can often not be contributed to colon cancer directly.

The post-operative complication rate reported in single center studies where chart review was conducted was much higher than the 4.3% described in the study by Neuman et al. which included its subjects through the SEER database. This is likely the result of underreporting of especially minor complications. [10-12,14] Thirty-day mortality rates were comparable. (Table 1)

Several methods have been developed to estimate the risk of complications in elderly patients undergoing major surgery. Marventano et al. suggested a modified version of the Charlson Comorbidity Index to predict overall and cancer specific survival in colorectal cancer patients. [16] The authors stressed that age should not be used to determine a patients eligibility for surgery, as age has a minor influence on post-operative complications and cancer specific survival. However, age is associated with overall survival and will help to predict the expected overall survival benefit of the patient after surgery. [17] Another study by Neuman et al. investigated predictors of mortality in elderly patients undergoing elective surgery for colon cancer. Frailty, defined through a scoring system, was by far the strongest predictor of 90-day mortality. [18] Similarly, Robinson et al. showed a "get up and go" test to be a strong predictor of post-operative morbidity and mortality with a 3% versus 31% 1-year mortality associated with a fast versus slow result. [19] When considering surgery, a laparoscopic procedure is preferable to an open resection resulting in fewer postoperative complications, a shorter hospital stay, and a lower in-hospital mortality. [20-23]

In conclusion, the considerable risk of peri-operative complications has to be weighed against survival benefit and the risk of need for an emergency intervention in the setting of obstruction. It is logical to assume that these risks are in equilibrium: A patient with a poor performance score has a high risk of peri-operative complications, but also a shorter life expectancy reducing the risk of obstruction of the bowel. Physical performance appears to be the strongest predictor of mortality. One-year survival is approximately 80% in the octogenarians currently being treated with surgery, with only 25% of mortality occurring in the month after surgery. Little is known about the outcomes and causes of death of those that choose conservative management.

ADJUVANT THERAPY FOR COLON CANCER

The benefit of adjuvant chemotherapy in patients with stage 3 colon cancer has been demonstrated in multiple RCT's. [24-28] Patients in these studies have a median age of 59-62 years, with some trials also posing restrictions on performance score. Conversely, over 50% of patients diagnosed with colon cancer in the Netherlands are at least 70 years of age. [29] Thus, it is difficult to extrapolate the findings of these studies to the general population. A meta-analysis of several RCT's comparing 5FU based regimens with placebo found no interaction between age and (disease free) survival. [30]

Some retrospective studies have been performed to investigate the benefit of adjuvant therapy in the elderly and the frail. (Table 2) However, they suffer from significant bias

Table 1. Post-operative outcomes in several retrospective studies:

Author	Publication year	Patient Age	treatment modality	N	Overall survival		Post-operative complications	30-day mortality
Damhuis [9]	2005	>80	Surgery	2765				10.60%
Latkauskas [10]	2005	>75	surgery	154	39%	5y OS	46%	11%
Devon [11]	2009	>75	surgery	272	57.3	5y OS	38%	4.2%*
Hermans [12]	2010	>75	surgery	74	42%	5y OS	50%	16%*
Faiz [8]	2011	>75	Surgery	28.746	82%	1y OS		5.40%
van Gestel [13]	2013	>75	surgery	2.008	88%	90d OS		8.30%
Neuman [7]	2013	>80	surgery	25.358	78%	1y OS	4.30%	3%
			conservative	6.216	56%	1y OS	na	
Lievre	2014	>80	surgery	176	65.3	median OS in months	25%	6.70%

*In hospital mortality. OS: overall survival

Table 2. Outcomes of adjuvant chemotherapy in several retrospective studies of stage 3 colon cancer:

Author	Publication Year	Patient age	treatment modality	N	Overall survival	
Iwashyna [35]	2002	Pt's >67y	Chemotherapy	1.802*	52.70%	5y OS
			No chemotherapy	1.802*	40.70%	5y OS
Wildes [36]	2010	Pt's >75y	Chemotherapy	255	70%	3y OS
			No chemotherapy	180	42%	3y OS
Sanoff [33]	2012	SEER cohort; Pt's >75y	Chemotherapy	1773	70%	3y OS
			No chemotherapy	2453	50%	3y OS
		NYSCR cohort; Pt's >75y	Chemotherapy	449	63%	3y OS
			No chemotherapy	549	53%	3y OS
		CanCORS cohort; Pt's >75y	Chemotherapy	63	78%	3y OS
			No chemotherapy	58	60%	3y OS
		NCCN cohort; Pt's >75y	Chemotherapy	110	87%	3y OS
			No chemotherapy	36	59%	3y OS
van Steenbergen [34]	2012	Pt's >75y	Chemotherapy	1373	56%	5y OS
			No chemotherapy	6678	28%	5y OS
Abraham [32]	2013	Pt's >75y	Chemotherapy	3745	55%	5y CSS
			No chemotherapy	8637	43%	5y CSS
van Erning [37]	2016	Pt's >70y	Chemotherapy	352	66%	5y OS
			No chemotherapy	630	37%	5y OS
Bergquist [31]	2016	Pt's >80y	Chemotherapy	3483	51%	5y OS
			No chemotherapy	4658	32%	5y OS

Results of studies by Zuckerman and Du are not shown as they as they are reported per age group. [38-39]
*: Propensity matched cohort, other results are unadjusted. OS: overall survival; CSS: cancer specific survival.

by indication. [31-39] Nonetheless, all of these studies point towards a survival benefit of adjuvant chemotherapy in even the oldest patients. Results are mixed when it comes to reporting an interaction between age and survival benefit of adjuvant chemotherapy. Zuckerman et al. reports an interaction while Wildes et al. do not. [36,39] The benefit of secondary prevention could be assumed to decrease with increasing age and in extension increased risk of death from competing causes. The lack of interaction then points toward a bias by indication despite propensity matching, most likely caused by the performance score of the patient for which these retrospective studies were not able to correct. This phenomenon is exacerbated in the oldest patients since a smaller percentage receives treatment. Despite this bias, it is likely that the patients treated with adjuvant chemotherapy experienced survival benefit. This is confirmed in the study by Bergquist et al. showing that patients who were offered adjuvant chemotherapy, but declined, had a worse survival than those who accepted. [31] Over the past decade, the use of

adjuvant chemotherapy in elderly patients in the Netherlands has steadily increased while outcomes have improved. [34] Nevertheless, It remains difficult to draw firm conclusions regarding patients who were previously deemed unfit to receive adjuvant therapy by their treating physicians. Considering the 20% 1-year mortality after surgery in octogenarians some restraint is warranted, especially in those with poor physical performance.

Clinicians often refrain from the addition of oxaliplatin to 5FU based regimens in the elderly due to a, perceived, increased toxicity and reduced survival benefit. Clinical studies showed mixed results. There are two meta-analyses of the subset of elderly patients included in several RCT's comparing oxaliplatin and non-oxaliplatin based regimens which show conflicting results [40,41] McClearly et al. demonstrated no benefit of oxaliplatin in patients 70 years and older while Haller et al. do. This benefit is less pronounced than it is in younger patients. This discrepancy could be explained by the fact that the study by Haller did not include the MOSAIC and the NSABP-07 trials, [25,42] which both showed a significant interaction between age and overall survival. Also, the study by McClearly only assessed interaction with age, while the study by Haller also included the Charlson comorbidity index. As before, the subset of patients included in these RCT's does not adequately reflect daily practice. A number of retrospective studies, likely containing frailer patients, found no statistically significant benefit of the addition of oxaliplatin to adjuvant therapy in patients over 70 years of age. [33,43,44] However, with the recent results of the IDEA collaboration demonstrating non-inferiority of 3 months of capecitabine oxaliplatin when compared to 6 months in patients without T4 or N2 disease, clinicians will be compelled to prescribe this regimen. [45] Whether oxaliplatin can be omitted in patients over 70 when prescribing a 3 month regimen is yet to be investigated.

Meta-analyses of previous RCT's conducted with 5-fluorouracil as well as oxaliplatin containing regimens show a slight increase in overall grade 3+ toxicity in patients over 70. Interestingly, no specific type of toxicity appears more prevalent in elderly patients. This includes neuropathy in patients receiving oxaliplatin. [27,30,46] Even so, the addition of oxaliplatin did lead to increased toxicity in all treated patients. [25-27] Another study examining different 5-fluorouracil regimens in advanced colorectal cancer showed performance score and the number of treatment cycles administered to be stronger indicators of toxicity. [47] Kahn et al. did not report an increase in adverse events (AE's) in a retrospective study. However, this finding did not correspond with the reported high discontinuation rate of chemotherapy among patients >65 years. [48] Two other retrospective cohort studies also showed no relation between incidences of AE's and age. [49,50] Regardless, some of the burden of toxicity will be removed with a shorter treatment course. [51]

The benefit of adjuvant chemotherapy in stage 2 colon cancer across all age groups is less clear. Large meta-analyses show mixed results when trying to ascertain the benefit to time to recurrence. [52-54] This is partly caused by the relatively good prognosis of stage 2 colon cancer. Thus, in elderly patients, where the expected survival benefit is even smaller due to an increase in competing causes of death, one might be even more conservative in administering adjuvant chemotherapy.

In conclusion, adjuvant chemotherapy improves overall survival in a selected population of elderly patients with stage 3 colon cancer. It does so without strong evidence of increased toxicity when compared to younger patients. Even so, all patient data originates from either meta-analysis of elderly patients who participated in RCT's or retrospective cohort studies. This introduces significant bias. Thus, it is hard to determine whether patient who are currently deemed unfit for adjuvant chemotherapy would benefit from or tolerate treatment. Performance score appears to be the most important predictor of a favourable outcome. It remains in the hands of the clinician to make an individualized decision for each patient.

CONCLUSIONS

It is difficult to draw firm conclusions about the treatment of elderly patients with colon cancer. Complicating factors are the lack of randomized controlled trials, and the large heterogeneity of this patient group. The observational studies that have been performed are troubled by selection bias and bias by indication. However, they do show positive results of treating elderly patients with surgery as well as adjuvant chemotherapy. Thus there is at least a subset of elderly patients that benefit from treatment. This review tries to quantify the risks and benefits of various therapies for the elderly patient. Which patients benefit is difficult to determine and requires careful clinical decision making. A bad performance score appears to be the most important determinant of a poor prognosis.

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Chapter 1

IMPACT OF AGE AND COMORBIDITY ON SURVIVAL IN COLORECTAL CANCER

E.E. van Eeghen
S.D. Bakker
A. van Bochove
R.J.L.F. Loffeld

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ABSTRACT

Introduction

Patients with colorectal cancer are often excluded from clinical trials based on age or a poor performance score. However, 70% of colorectal cancer is diagnosed in patients over 65.

Aim

Evaluation on the influence of age and comorbidity on survival and cause of death in a non-selected population.

Patients and methods

Included were 621 consecutive patients with colorectal cancer. An extensive chart review was performed for 392 patients with colon cancer and 143 patients with rectal cancer. Analyses were performed separately for both groups.

Results

Median survival of colon cancer patients was 5.13 years, 131 patients (34.3%) died from tumour progression. Age and comorbidity were significant predictors for overall survival ($p<0.001$). Age was also a significant predictor of cause of death ($p=0.001$). In rectal cancer patients median survival was 4.67 years, 51 (35.7%) of patients died from tumour progression. Neither age nor comorbidity was significant predictors of survival. Age was a significant predictor of cause of death ($p<0.001$).

Conclusion

In colon cancer patient age and comorbidity predict survival. This represents possible bias or a reduced survival benefit of treatment, and is an indication that colon cancer is not the prognosis defining illness in the majority of patients. In rectal cancer patients neither age or comorbidity significantly impacted survival.

INTRODUCTION

Colorectal cancer is the third most occurring malignancy in the Netherlands with over 13000 new cases in 2012. Seventy percent of these patients are above the age of 65 years, and 21% is even older than 80 years of age.[1] Despite the high prevalence of colorectal cancer in the elderly population, the inclusion of this cohort in clinical trials is disproportionately low. In addition, inclusion is limited to patients with little comorbidity and a high performance score.[2-4] Hence, it is questionable whether the evidence for treatment of colorectal cancer is valid in a large percentage of patients. As such, Dutch guidelines recommend individualised treatment and emphasize shared decision making in elderly patients with comorbidity.[5]

A number of studies have been performed analysing the influence of age and comorbidity on outcomes as well as decisions by clinicians whether to treat patients with chemotherapy in adjuvant or palliative setting. A number of observational studies show survival benefit of chemotherapy treatment in elderly patients.[6-9] Survival, and the survival benefit of treatment is reduced with increasing age and comorbidity.[10,11] Also, the percentage of patients treated with chemotherapy is inversely correlated with age and comorbidity.[12]

Due to their retrospective nature, and the fact that standard treatment is withheld in a large portion of elderly patients based on their comorbidity and performance score, studies examining the relation between comorbidity and treatment efficacy suffer from selection bias. The present cross-sectional single centre study examines the effect of age and comorbidity on survival. In addition, cause of death was evaluated as colorectal cancer patients do not die exclusively because of cancer.

METHODS

All consecutive patients diagnosed and treated for colorectal cancer within a specific timeframe (2002 – 2008) in the Zaans Medisch Centrum, the community hospital of the Zaanstreek region in the Netherlands, were included. An extensive chart review was performed for all these patients. Via detailed patient information transparency was increased, and bias in the assessment of the effect of comorbidity on outcomes could be minimised.

Evaluation was done on 1-1-2014. The review consisted of an examination of patient charts with medical history, pathology, radiology, and endoscopy reports as well as data from the department of pharmacy. [13]

The well-known Charlson comorbidity score was used to estimate comorbidity. The diagnosis of colorectal cancer was excluded in the calculation of the Charlson index.[14-16] Overall survival was measured from date of diagnosis till date of death. The TNM7 classification was used to assess disease stage. [17] A detailed description of all variables and exclusions are noted in the appendices.

Kaplan Meier curves for overall survival were calculated, separate for both age, categorized into 4 equally sized groups, and Charlson index, divided into 3 categories: 0 (1), 1-2 (2), and 3+ (3). Uni- and Multivariable cox regression analysis was used to assess hazard ratios of survival for age, comorbidity score and tumour characteristics. Poisson regression was used to determine the risk ratio of dying due to tumour progression relative to death from other causes. Separate analyses were performed for patients with rectal and colon cancer.

Statistical analyses were performed using IBM SPSS statistics software version 20.0 and Microsoft Office Excel 2010.

The study was approved by the ethical committee of the Zaans Medisch Centrum.

RESULTS

Six hundred twenty-one patients were diagnosed with colorectal cancer between 1-1-2002 and 31-12-2008. Eighty-six patients were excluded for various reasons. See Tables S1 and S2 for detailed descriptions of these exclusions. These patients were referred to a nearby University Hospital for treatment on their own request. Follow-up data of all patients were present for a minimum of five years and a maximum of thirteen years, depending on the year of inclusion, or until death.

Colon

Three hundred ninety-two patients were diagnosed with colon cancer. Median follow up was 5.13 years, interquartile range (iqr) 1.17 – 7.42. One hundred sixty-five patients (42.1%) were alive at the end of follow up. One hundred thirty-one patients (33.4%) died from tumour progression, 23 patients (5.9%) experienced treatment related adverse events with fatal outcome and 51 patients (13.0%) died from other causes. Median age at diagnosis was 71.6 years, iqr 63.3 – 79.5. Mean Charlson index was 0,82, range 0 - 7 (tables 1a and 1b)

Age at the time of diagnosis and Charlson comorbidity index were significant predictors of survival in uni- and multivariable cox regression analysis ($p<0.05$). Hazard ratio (HR) of death in multivariable analysis for age was 1.019 per year increase. For comorbidity the HR was 1.218 per point increase on Charlson score (figures 1 and 2, table 3)

Age and comorbidity index were also significant predictors of death from causes other than tumour progression in multivariate analysis. Risk ratio (RR) for death from other causes was 1.041 per year of age. The RR increased 1.162 per point increase in Charlon score (table 2).

Rectum

One hundred forty-three patients were diagnosed with rectal cancer. Median follow up was 4.51 years, iqr 1.67 – 7.26. Forty-nine patients (34.3%) were alive at the end of follow up. Fifty-one patients (35.7%) died from tumour progression, 12 patients (8.4%)

Table 1a. Influence of charlson score on survival and cause of death in colon cancer

Charlson score		0		1-2		3+		Total	
Total		217		139		36		392	
Gender	male	102	47.00%	78	56.10%	26	72.20%	206	52.60%
	female	115	53.00%	61	43.90%	10	27.80%	186	47.40%
Median survival (iqr)		5.67	1,54 - 7,76	4.17	0,67 - 6,84	2.33	0,71 - 5,76	5.13	1,17 - 7,42
1-year survival		174	80.20%	101	72.70%	26	72.20%	301	76.80%
5-year survival		131	60.40%	63	45.30%	11	30.60%	205	52.30%
Cause of death	Tumor progression	74	34.10%	45	32.40%	12	33.30%	131	33.40%
	Tx	9	4.10%	11	7.90%	3	8.30%	23	5.90%
	Other	17	7.80%	23	16.50%	11	30.60%	51	13.00%
	Unknown	8	3.70%	11	7.90%	3	8.30%	22	5.60%
	Alive	109	50.20%	49	35.30%	7	19.40%	165	42.10%
	Other+Tx/(other+Tx+tumor progression)	26/100	26.00%	34/79	43.00%	14/26	53.80%	74/205	36.10%
Median Age (iqr)		67.0	59.8 - 76.9	75.1	69.0 - 80.4	75.9	69.2 - 83.3	71.6	63.3 - 79.5
TNM stage	0-1	24	11.20%	22	15.90%	5	14.70%	51	13.20%
	2	79	36.90%	55	39.90%	14	41.20%	148	38.30%
	3	56	26.20%	31	22.50%	8	23.50%	95	24.60%
	4	55	25.70%	30	21.70%	7	20.60%	92	23.80%

Table 1b. Influence of age on survival and cause of death in colon cancer

Age		- 63,26		63,26 - 71,61		71,61 - 79,49		79,49 -		Total	
Total		98		97		99		98		392	
Gender	male	54	55.10%	61	62.90%	53	53.50%	38	38.80%	206	52.60%
	Female	44	44.90%	36	37.10%	46	46.50%	60	61.20%	186	47.40%
Median survival (iqr)		5.67	1,50 - 7,78	5.51	1,58 - 8,13	5.09	1,33 - 7,34	3.42	0,42 - 6,51	5.13	1,17 - 7,42
1-year survival		82	83.70%	75	77.30%	79	79.80%	65	66.30%	301	76.80%
5-year survival		57	58.20%	57	58.80%	51	51.50%	40	40.80%	205	52.30%
Cause of death	Tumor progression	39	39.80%	31	32.00%	31	31.30%	30	30.60%	131	33.40%
	Tx	2	2%	7	7.20%	3	3%	11	11.20%	23	5.90%
	Other	4	4.10%	7	7.20%	23	23.20%	17	17.30%	51	13.00%
	Unknown	4	4.10%	3	3.10%	4	4.00%	11	11.20%	22	5.60%
	Alive	49	50.00%	49	50.50%	38	38.40%	29	29.60%	165	42.10%
	Other+Tx/(other+Tx+ tumor progression)	6/45	13.30%	14/45	31.10%	26/57	45.60%	28/58	48.30%	74/205	36.10%
Mean Charlson score		0.42		0.69		1.05		1.12		0.82	
TNM stage	0-1	8	8.20%	15	15.60%	14	14.10%	14	14.90%	51	13.20%
	2	34	35.10%	29	30.20%	40	40.40%	45	47.90%	148	38.30%
	3	28	28.90%	25	26.00%	26	26.30%	16	17.00%	95	24.60%
	4	27	27.80%	27	28.10%	19	19.20%	19	20.20%	92	23.80%

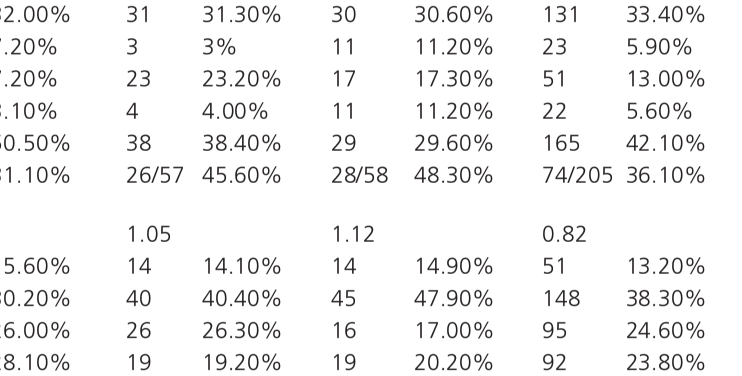

figure 1. KM plot of colon cancer survival based on Age category

Frequency table

	0	1	2	3	4	5	6	7	8	9	10
1	98	82	72	63	61	57	48	36	22	14	8
2	97	75	69	64	60	57	44	32	27	18	5
3	99	79	64	60	54	51	36	26	14	7	6
4	98	65	57	51	45	40	31	21	13	11	4

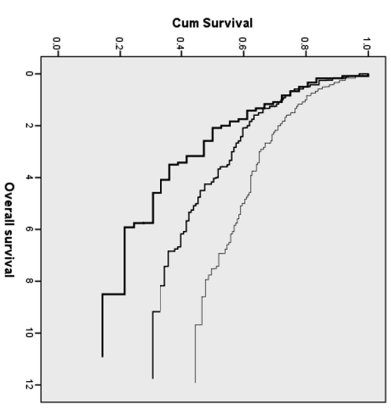

Figure 2. KM plot of colon cancer survival based on Charlson index category

Frequency table

	0	1	2	3	4	5	6	7	8	9	10
1	217	174	156	142	135	131	105	77	48	33	14
2	139	101	86	79	72	63	47	34	25	16	8
3	36	26	20	17	13	11	7	4	3	1	1

Table 2a. Influence of charlson score on survival and cause of death in rectal cancer

Charlson score		0		1-2		3+		Total	
Total		85		47		11		143	
Gender	Male	46	54.10%	31	66.00%	7	63.60%	84	58.70%
	Female	39	45.90%	16	34.00%	4	36.40%	59	41.30%
Median survival (iqr)		5.91	2,71 - 7,84	3.17	1,00 - 6,50	1.75	1,34 - 6,26	4.67	1,67 - 7,34
1-year survival		74	87.10%	36	76.60%	10	90.90%	120	83.90%
5-year survival		46	54.10%	20	42.60%	4	36.40%	70	49.00%
Cause of death	Tumor progression	30	35.30%	18	38.30%	3	27.30%	51	35.70%
	Tx	6	7.10%	5	10.60%	1	9.10%	12	8.40%
	Other	12	14.10%	5	10.60%	3	27.30%	20	14.00%
	Unknown	6	7.10%	4	8.50%	1	9.10%	11	7.70%
	Alive	31	36.50%	15	31.90%	3	27.30%	49	34.30%
	Other+Tx/(other+Tx+ tumor progression)	18/48	37.50%	10/28	35.70%	4/7	57%	32/83	38.60%
Median Age (iqr)		65.7	59,5 - 76,6	72.6	66,5 - 81,5	64.3	60,6 - 75,7	68.0	61,3 - 78,1
TNM stage	0-1	14	17.50%	5	11.60%	0	0.00%	19	14.30%
	2	27	33.80%	12	27.90%	6	60.00%	45	33.80%
	3	22	27.50%	14	32.60%	2	20.00%	38	28.60%
	4	17	21.20%	12	27.90%	2	20.00%	31	23.30%

Table 2b. Influence of age on survival and cause of death in rectal cancer

Age		- 61,27		61,27 - 67,98		67,98 - 78,06		78,06 -		total	
Total		36		35		36		36		143	
Gender	Male	23	63.90%	22	62.90%	23	63.90%	16	44.40%	84	58.70%
	Female	13	36.10%	13	37.10%	13	36.10%	20	55.60%	59	41.30%
Median survival (iqr)		3.79	1,96 - 6,61	5.09	1,75 - 7,51	4.54	1,63 - 7,99	5.55	1,04 - 7,90	4.67	1,67 - 7,34
1-year survival		32	88.90%	30	85.70%	30	83.30%	28	77.80%	120	83.90%
5-year survival		17	47.20%	18	51.40%	16	44.40%	19	52.80%	70	49.00%
Cause of death	Tumor progression	16	44.40%	14	40.00%	14	38.90%	7	19.40%	51	35.70%
	Tx	2	5.60%	4	11.40%	3	8.30%	3	8.30%	12	8.40%
	Other	1	2.80%	2	5.70%	3	8.30%	14	38.90%	20	14.00%
	Unknown	4	11.10%	2	5.70%	4	11.10%	1	2.80%	11	7.70%
	Alive	13	36.10%	13	37.10%	12	33.20%	11	30.60%	49	34.30%
	Other+Tx/(other+Tx+ tumor progression)	3/19	15.80%	6/18	33.30%	6/20	30.00%	17/24	70.80%	32/83	38.60%
Mean Charlson score		0.64		0.63		1.00		0.89		0.79	
TNM stage	0-1	4	11.80%	4	11.80%	4	11.40%	7	23.30%	19	14.30%
	2	12	35.30%	13	38.20%	9	25.70%	11	36.70%	45	33.80%
	3	6	17.60%	7	20.60%	16	45.70%	9	30.00%	38	28.60%
	4	12	35.30%	10	29.40%	6	17.10%	3	10.00%	31	23.30%

IMPACT OF AGE AND COMORBIDITY ON SURVIVAL IN COLORECTAL CANCER

experienced treatment related adverse events with a fatal outcome, and 20 patients (14.0%) died from other causes. Median age at diagnosis was 68.0, iqr 61.3 – 78.1. Mean Charlson index was 0.79, range 0-8 (Tables 2a and 2b).

There was a trend towards increased risk of death per point increase in comorbidity score, HR 1.108 (95% CI 0.967 – 1.270). Hazard ratio's determined for age at diagnosis was not valid as the proportional hazards assumption was not met. This is most likely due to a small effect size (figures 3 and 4, table 3).

Age at diagnosis was a significant predictor of cause of death in multivariate analysis with a RR of 1.012 per year of age to die from causes other than tumour progression. The comorbidity index was not a significant predictor of cause of death (table 4).

DISCUSSION

This study deals with the impact of age and comorbidity on overall survival and cause of death in patients diagnosed with colorectal cancer in normal daily practice.

Eighteen patients were referred to a tertiary centre for treatment mostly at their own request. A possible limitation of the present study is the relatively small sample size when comparing it to others in its field using large patient registries. However, the strength of the present study is the introduction of cause of death in the analysis.

This study has a long follow up period, with (near) perfect follow up for the first five years. In addition, since all consecutive patients were included, this study accurately represents the population of colorectal cancer patients in a developed country in normal daily practice. Furthermore, patient and tumour characteristics are extensively documented. To our knowledge this is the first study to include causes of death, tumour characteristics and a comorbidity measure in a study of colorectal cancer survival.

In colon cancer patients, age and comorbidity are predictors of survival. This solidifies the notion that despite the morbidity and mortality associated with a colon cancer diagnosis; baseline patient characteristics still largely predict a patient's primary outcome. This underlines the need to treat patients holistically.

Age is also significantly associated with cause of death, with a difference of 35% (48% vs 13%) in ratio between death from tumour progression and other causes. This is primarily caused by an increase in death from other causes as the percentage of patients dying due to tumour progression remains constant. However, one should take into account that with increasing age, overall survival, and thus follow up, decreases, as does the intensity of cancer treatment. [18,19] This has also been observed for adjuvant therapy in this cohort. [13]

The observation that cancer related mortality does not decrease with increasing age exemplifies the idea that, although elderly patients have a shorter life expectancy based on their age and pre-existent conditions, they do still benefit from cancer treatment. However, this survival benefit is hard to quantify. The present study does not take associated morbidity and quality of life into account. Therefore a shared decision making model when treating elderly patients with colon cancer is advocated.

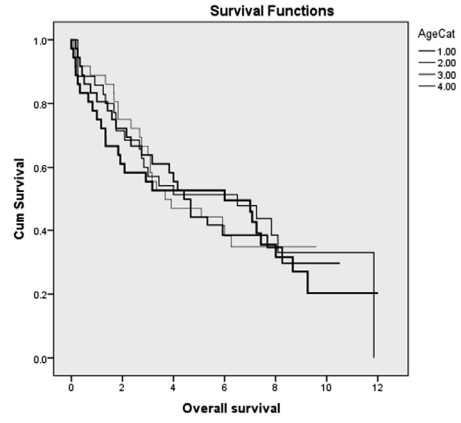

Figure 3. KM plot of rectum cancer survival based on age category

Frequency table

	0	1	2	3	4	5	6	7	8	9	10
1	36	32	27	24	17	17	13	8	2	1	0
2	35	30	25	21	19	18	16	12	7	2	1
3	36	30	26	23	21	16	12	10	9	3	1
4	36	28	22	20	19	19	17	14	9	5	2

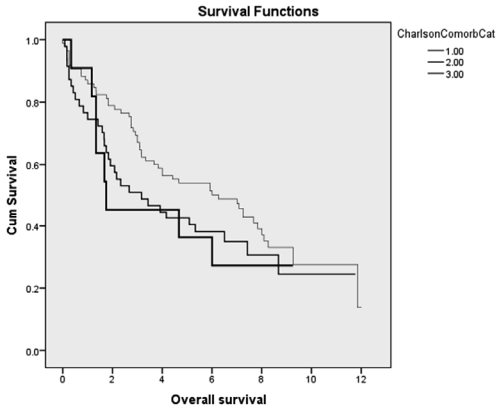

figure 4. KM plot of rectum cancer survival based on charlson index category

Frequency table

	0	1	2	3	4	5	6	7	8	9	10
1	85	74	67	59	50	46	40	33	20	7	3
2	47	36	28	24	21	20	14	9	6	3	1
3	11	10	5	5	5	4	4	2	1	1	0

Table 3. Cox regression analysis for overall survival

	Colon				Rectum			
	Univariable		Multivariable		Univariable		Multivariable	
	HR for death	95% CI	HR for death	95% CI	HR for death	95% CI	HR for death	95% CI
Age at diagnosis (continuous)	1.023	1.010 - 1.037	1.019	1.005 - 1.033	***			
Cormorbidity index (continuous)	1.254	1.140 - 1.381	1.218	1.102 - 1.346	1.109	0.968 - 1.271	1.108	0.967 - 1.270

***Failed proportional hazards assumption, see figure 3 for KM plot. Still included in multivariable analysis

Table 4. Poisson regression analysis for death from other causes and treatment relative to death from tumor progression.

	Colon				Rectum			
	Univariable		Multivariable		Univariable		Multivariable	
	RR for death from other causes	95% CI	RR for death from other causes	95% CI	RR for death from other causes	95% CI	RR for death from other causes	95% CI
Age at diagnosis (continuous)	1.043	1.025 - 1.061	1.041	1.022 - 1.059	1.013	1.007 - 1.019	1.012	1.006 - 1.019
Comorbidity index (continuous)	1.202	1.079 - 1.339	1.162	1.019 - 1.327	1.030	0.985 - 1.078	1.020	0.980 - 1.061

In this study, rectal cancer patients' age and comorbidity did not significantly influence survival or the cause of death. The explanation could be that cancer related mortality in this cohort was very high, implicating that all patients should be treated according to standard guidelines irrespective of age or pre-existent conditions.

However, the validity of these findings is questionable. First off, the findings do not correspond with previous large cohort studies that did find an inverse relationship between age and comorbidity, and survival. [20,21] The tumour related mortality in our rectal cancer is almost identical to that of colon cancer in our cohort (33.4% (colon) vs 35.7% (rectum)). The median survival of 4.67 years of rectum cancer patients is also similar to that of the colon cancer patients in this cohort and corresponds with the 5 year survival rate of approximately 50% observed in the study by Ostenfeld et al. in the same time period.[11]

Thus, one could conclude that the non-significant effect of the Charlson score on survival likely represents a small sample size and a type 2 error as the Charlson score has been validated to predict overall survival in many much larger cohorts [22,23], and, as just established, it is unlikely that the effect of comorbidity is negated by a higher cancer related mortality in this cohort.

In conclusion, age and comorbidity are significant predictors of overall survival, reflecting the importance of optimizing patients beyond their cancer treatment, and cause of death. This represents possible treatment bias and a reduced survival benefit of treatment with increasing age. In rectal cancer patients neither comorbidity nor age was a predictor of overall survival. This could be explained if rectal cancer was the prognosis defining illness in the majority of cases, however this is contradicted by the observed median survival and the percentage of cancer related deaths. As such, the validity of these outcomes can be questioned.

We recommend further study of the benefit of cancer treatment in the elderly, and advocate inclusion of this patient group in clinical trials.

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Chapter 2

COLORECTAL CANCER IN OCTOGENARIANS: RESULTS OF TREATMENT

E.E. van Eeghen
S.D. Bakker
R.J.L.F. Loffeld

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ABSTRACT

Background

Colorectal cancers (CRC) occur in octogenarians. Data on treatment and survival are sparse. Octogenarians were studied in order to gain data on treatment, outcome, and survival.

Methods

All consecutive octogenarians with CRC in the time-period 2002-2008 were included. An extensive review of hospital records was done. Patients were divided in group 1: patients who were alive after five years of follow-up, and group 2: patients deceased within 5 years after diagnosis. Cause of death was determined and classified as related to cancer, non-related or because of treatment.

Results

111 octogenarians were diagnosed with CRC (82 colon cancers and 29 rectal cancers). Patients in group 2 had a significantly higher disease stage compared with group 1 ($p<0.001$). Patients in group 1 underwent more often surgery with curative intent ($p<0.0001$). There was no difference in clinical presentation or localization of the malignancy. In group 1 fourteen patients died more than five years after surgery. The cause of death was not related to cancer in 100% of cases. In group 2 29 (46.0%) died as a direct consequence of the CRC, 14 (22.2%) due to the treatment, and 20 (31.7%) died due to non-cancer related causes. Overall five year survival was 40% in colon cancer and 51.7% in rectal cancer. Charlson age co-morbidity score was significantly lower in colon cancer patients of group 1 ($p = 0.005$). This was not the case in patients with rectal cancer.

Conclusion

Co-morbidity score is important in survival after surgery. Forty four percent of octogenarians with colorectal cancer died because of non-tumour related disease or illness. Fit elderly can benefit from standard therapy for colorectal cancer.

INTRODUCTION

Colorectal cancer is one of the most occurring malignancies in the Western World. Since people have a longer life expectancy this type of cancer will also occur in octogenarians. Colonoscopy is the best diagnostic modality. In patients 80 or more years of age it is a safe and effective procedure with a high diagnostic yield [1]. There also is a significant higher yield compared with patients younger than 80 years [2]. In a previous study done in the Zaanstreek region it was shown that 20% of the colorectal cancers occurred in patients above the age of 80 years. This number stayed rather constant in a period of 18 consecutive years [3].

Patients above the age of 80 years are excluded from large clinical trials. They do not have the potential life expectancy to gain enough follow-up years after treatment. However, in normal daily practice the clinician has to deal with octogenarians and has to decide on the best treatment option. Surgery is the only curative treatment. But, many older patients are frail, have significant co-morbidity and are at risk for any type of surgery. Retrospective series show that older patients can have the same benefit from optimum treatment strategies as their younger counterparts. Lack of prospective data and increased toxicity rates seen in older patients lead to reluctance to treat older patients adequately [4].

Little data is present in the literature on the treatment and especially outcome of treatment of colorectal cancer in octogenarians. For this reason a study was done in consecutive octogenarians in order to gain data on treatment, outcome, and disease free survival.

PATIENTS AND METHODS

All consecutive patients older than 80 years diagnosed with colorectal cancer in the Zaans Medical Centre, the community hospital of the Zaanstreek region in the Netherlands were included. The study period started in 2002 and ended in 2008. Evaluation was done in January 2014. Hence, there was at least five years of follow-up for every patient.

An extensive review of all hospital records (clinical files, endoscopy reports, and pathology reports) was done in order to study the presentation of the malignancy, disease stage (Dukes classification), treatment, recurrence, recurrence free survival, and overall survival. In addition, co-morbidity was scored using the well-known Charlson age co-morbidity score [5,6,7].

For the sake of the study patients were divided in two groups. Group 1: patients who were alive after five years of follow-up, and group 2: patients who died within 5 years after diagnosis and treatment. Cause of death was determined and classified as related to cancer, non-related or because of treatment.

Statistical analysis was done with chi-square test for contingency tables and with t-test. A value below 0.05 was considered statistical significant.

RESULTS

In the time period from 2002-2008 a total of 111 octogenarians were diagnosed with colorectal cancer (82 patients with colon cancer and 29 with rectal cancer). Table 1 shows the characteristics of the patients. There was no difference in gender between both groups. Patients in group 2 had significantly more often a higher stage of disease compared with the group of long survivors (p<0.001). In group 1, a higher percentage of patients underwent surgery with curative intent (p<0.0001). There was no significant difference in clinical presentation, in the sense of principal complaints, between both groups of patients. There was no difference in localization of the cancer between both groups.

In group 1 fourteen patients died more than five years after surgery. The cause of death was not related to cancer in 100% of cases. In group 2 all patients died within five years after the diagnosis. Twenty nine (46.0%) as a direct consequence of the colorectal cancer, 14 (22.2%) due to the complications of treatment, and finally 20 (31.7%) patients died due to non-cancer related causes. Non-cancer related death was 28.7% in patients with colon cancer and 42.9% in patients with rectal cancer. There was no significant difference between patients with colon cancer or rectal cancer. Overall five year survival was 33 out of 82 (40%) patients with colon cancer and 15 out of 29 (51.7%) patients with rectal cancer. Figures 1 and 2 show the survival curves with overall survival but also cancer specific survival. There is no difference for colon or rectum. Figure 3 shows the time to recurrence of patients with colon cancer. In group 2 patients with rectal cancer there was only one patient who had recurrent disease 1.98 year after diagnosis, the other four already had metastases at time of presentation.

Charlson age co-morbidity score was significantly lower in colon cancer patients of group 1; mean 5.73 (SD 0.94) versus 6.59 (SD 1.53) (p = 0.005). This was not the case in patients with rectal cancer; mean 5.73 (SD 0.88) versus mean 6.5 (SD 1.4) (p = ns).

None of the patients was treated with adjuvant chemotherapy in case of colon cancer, but 10 patients with rectal cancer and a survival exceeding five years were treated with neo adjuvant radiotherapy in comparison with only two patients who died within five years.

DISCUSSION

It can be expected that the number of octogenarians with colorectal cancer will rise. In the United States nearly 8% of all cancers diagnosed and 15% of cancer deaths occurred in individuals aged 85 years and older [8,9]. However, probably due to the increasing number of adenomas that have been removed endoscopically, it also can be expected that the number of colorectal cancers in octogenarians ultimately will decline in the future [2,3].

The present study describes the clinical course in octogenarians diagnosed with colorectal cancer. And, more specifically survival after diagnosis. All patients with

Table 1. Comparison of octogenarians with a follow-up of more than five years (group 1) and those who died within five years after diagnosis (group 2). The number between brackets is the percentage.

	Group 1	Group 2
N	48	63
Men	19(39.5)	28(44.4)
Women	29(60.5)	35(55.6)
	P = ns	
Causes of death		
Tumor related	-	29(46)
Treatment related	-	14(22.2)
Non-cancer related	14(100)	20(31.7)
Dukes A	11(22.9)	5(7.9)
Dukes B	28(58.3)	18(28.5)
Dukes C	7(14.6)	13(20.6)
Dukes D	-	17(26.9)
Unknown	1(4.2)	10(16.4)
	P<0.0001	
Curative surgery	47(97.9)	40(63.5)
	P<0.0001	
Lokalisation of the tumour		
Rectum	15(31.2)	14(22.2)
Sigmoid	15(31.2)	13(20.6)
Descending colon	-	1(1.6)
Transverse colon	5(10.4)	7(11.1)
Ascending colon	6(12.5)	9(14.3)
Coecum	7(14.7)	19(30.2)
	P = ns	
Complaints		
Bleeding	26(54.2)	20(31.7)
Anaemia	19(39.6)	32(50.8)
Abdominal pain	15(31.3)	23(36.5)
Changing bowel habits	21(43.7)	32(50.8)

colorectal cancer are discussed in a multi-disciplinary meeting with gastroenterologists, oncologists, surgeons, radiologists, and radiotherapists. On basis of clinical presentation, data from the literature and co-morbidity the best therapeutic option is chosen.

Obviously, as clearly shown, the disease stage in older patients with colorectal cancer is an important predictor of survival [10].

The present study shows that co-morbidity expressed as the Charlson age co-morbidity score is important in survival after surgery. However, this was only the case in patients

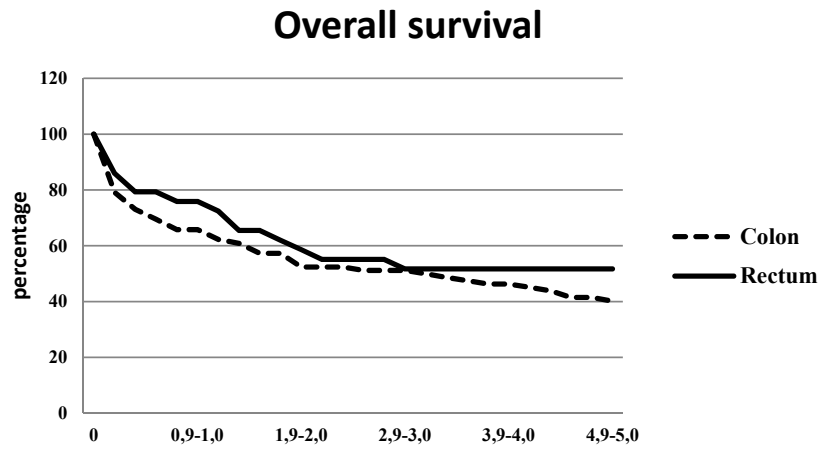

Figure 1. the survival curve of patients with colon and rectal cancer.

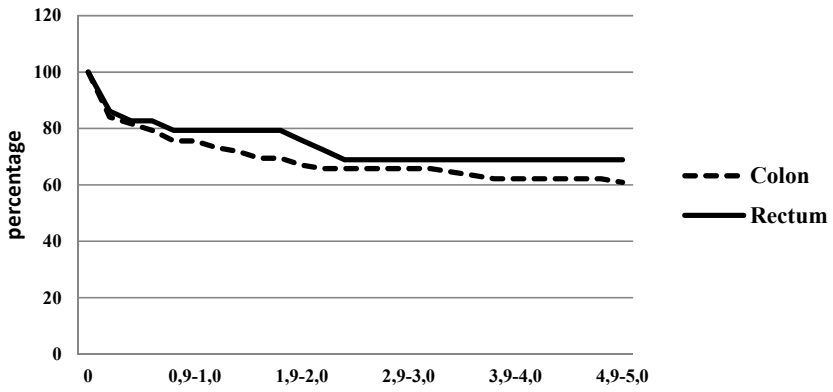

Figure 2. Cancer specific death in patients with colon and rectal cancer.

with colon cancer. Patients with rectal cancer have a longer or shorter survival after diagnosis irrespective of the Charlson age co-morbidity score. Why this is the case is not clear. This could be due to the small sample size. However, 10 out of 15 patients (67%) with rectal cancer underwent neo-adjuvant radiotherapy followed by surgery and were still alive after five years of follow-up in comparison with 2 out of 14 patients (14%) who died within the five years. This indicates that neo-adjuvant radiotherapy in cases of treatable rectal cancer, this is a lower clinical stage, has fair results in the octogenarians. This is in accordance with another study [11].

None of the octogenarians with colon cancer received adjuvant chemotherapy. According to the literature, receiving adjuvant chemotherapy is a poor factor of overall survival for older patients with colorectal cancer [11]. In a study adjuvant 5FU-based

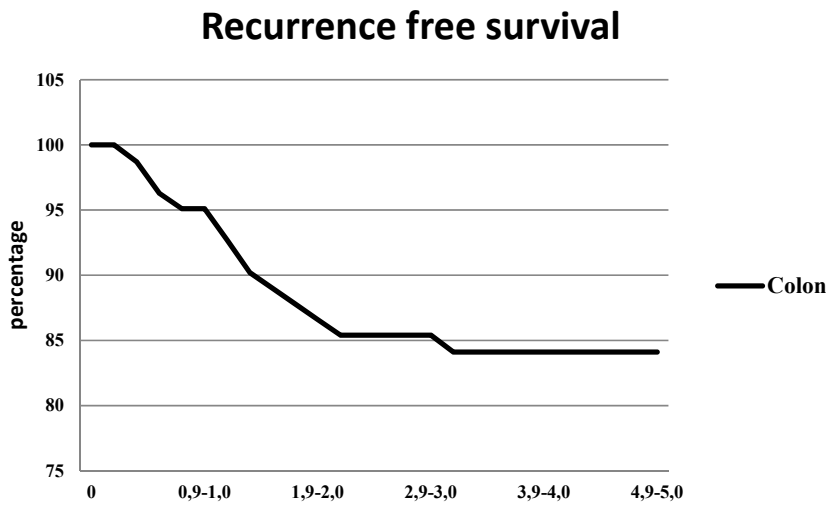

Figure 3. recurrence free survival of patients with colon cancer.

chemotherapy did not benefit older cancer patients, while neo-adjuvant radiotherapy improved the prognosis of older patients with stage III rectal cancer. [11]. However, there are also different opinions in the literature. Several publications suggest that geriatric patients can benefit from chemotherapy similarly to younger patients in the settings of both early- and advanced-stage colorectal cancer [12].

Another interesting point in the present study is that 31.7% of octogenarians with colorectal cancer died because of non-tumour related disease or illness. This certainly shows the limited life expectancy of elderly patients with co-morbidity. This is in accordance with another study from the Netherlands [13]. On the other hand, the prognosis of patients with colorectal cancer who underwent curative surgery improves with each additional year survived, with the largest improvements in the first years after diagnosis [13].

Management of cancer in elderly is challenging and screening patients in the 80+ age group. Older patients with colorectal cancer are under-represented in clinical trials. For that reason the outcomes in elderly are unclear. A reduced life-expectancy should lead to more conservative approaches. Treatment outcomes for fit, elderly patients with colorectal cancer can be similar to those of younger patients as shown in the present study. A consensus report expressed the hope that recommendations will pave the way for formal treatment guidelines based upon scientific evidence in the future [14].

Screening for frailty is useful. A study showed one-year survival to be 80% in the frail group and 92% in the non-frail group. Five-year survival was significantly lower in frail (24%) than non-frail patients (66%) [15]. A palliative approach should be taken in consideration for frail elderly patients and for those with a short life expectancy [16]. Data from studies specifically targeting older patients indicate that proper treatment planning and specific medical and geriatric assessment can achieve a safe and beneficial

treatment result in older patients [17]. Chronological age should not be an exclusion criterion for therapy. Careful patient selection, dose adjustments, close monitoring and early intervention in the event of side effects are essential [17]. It is important to realize that 22% of patients died because of treatment related causes. Complications of surgery have a higher impact in frail patients.

In normal daily practice the most important question is whether the life expectancy of the patient is long enough. Sometimes treatment can be expected to be more hazardous than the original tumour. But if fit elderly are treated according to the standard applied in younger patients the results can be beneficial. The benefits of treatment must be balanced with potential side-effects of treatment and patients' wishes.

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Chapter 3

THIRTY DAYS POST-OPERATIVE MORTALITY AFTER SURGERY FOR COLORECTAL CANCER

E.E. van Eeghen
F.C. den Boer
R.J.L.F. Loffeld

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ABSTRACT

Introduction

The goal of surgery for colorectal cancer is cure. Unfortunately post-operative mortality occurs.

Aim

Identify co-morbidity and causes of mortality in the post-operative period in relation to direct technical complications of surgery.

Patients and methods

All consecutive patients who underwent surgery for colorectal cancer were included. Co-morbidity was determined via the Charlson co-morbidity score. The post-operative course was studied and cause of death within 30 days was determined. Patients were divided in two groups: group 1 died within 30 days after surgery and group 2 survival for longer than 30-days.

Results

Twenty three out of 333 patients (6.9%) with colon cancer and 6 out of 112 (5.3%) with rectal cancer died in the post-operative period. Patients in group1 were significantly older than patients in group 2 ($p<0.001$). Patients in group 1 with colon cancer also significantly had more often a higher stage of cancer ($p=0.03$). The Charlson co-morbidity score for patients with colon cancer in group 1 was mean 5.17 (SD 1.57, range 1-8), and for rectal cancer mean 4.83 (SD 2.32, range 2-7). There was no difference in Charlson co-morbidity score when patients from group 1 and 2 were compared. In group 1 13 (44%) died as a direct consequence of technical surgical complications. Sixteen patients died due to complications because of pre-existing co-morbidity.

Conclusion

Post-operative mortality very often is the direct result of pre-existing co-morbidity and not such much the direct result of the surgical procedure.

INTRODUCTION

Colorectal cancer is one of the most occurring malignancies, at least in the Western world.[1-4] The only curative option is surgery and post-operative mortality should be minimized. Post-operative events ultimately leading to death of the patient, of course are very frustrating for the entire surgical and medical team. Since many patients with colorectal cancer are older,[5] it is to be expected that an increasing number of patients have co-morbidity rendering any operation more hazardous. Even in cases of successful surgery, patients can die due to complications induced by their co-morbidity.

Many pre-operative scoring systems are used in order to identify patients at risk. Although data on post-operative mortality of colorectal surgery are well-known, little is known about the effect of co-morbidity and the direct causes of post-operative mortality. A large study from the department of Surgery from the Zaans Medical Centre clearly showed that the strongest predictors of in-hospital mortality were emergency surgery, tumor stage, age, pulmonary failure and cardiac failure.[6] But data on post-operative death due technical failure of surgery are not known. For this reason a study was done in consecutive patients operated upon because of colorectal cancer in order to identify causes of mortality in the post-operative period, and more specifically assess the technical failure of the operation.

PATIENTS AND METHODS

All consecutive patients who underwent surgery for colorectal cancer in the Zaans Medical Centre, the community hospital of the Zaanstreek region in the Netherlands, in the time period of 2002-2008, were included. An extensive chart review was done in order to identify co-morbidity of each individual patient. Co-morbidity for each patient was expressed as the Charlson age-comorbidity score. This score adds up points for each accompanying illness or condition together with a score for age. The diagnosis of cancer obviously was excluded in the calculation of this score.[7-9]

The post-operative course of each surgical patient was studied and the cause of death within 30 days after surgery was determined. Age of the patients, as well as localization of the tumor and cancer stage was noted as well. Patients were divided into two groups. Patients in group 1 died within 30 days after surgery (the post-operative mortality group), and patients in group 2 survived (the majority being operated upon) for longer than 30-days.

Statistical analysis was done with chi square test for contingency tables and t-test. A value below 0.05 was considered statistically significant.

RESULTS

A total of 392 patients with colon cancer and 145 patients with rectal cancer were diagnosed. Fifty nine patients with colon cancer and 34 with rectal cancer did not undergo surgery mostly because of metastatic disease (stage 4). Twenty three out of 333

patients (6.9%) with colon cancer died within the post-operative period of 30 days. This was 6 out of 112 patients (5.3%) with rectal cancer.

Patients in group 1 with colon cancer were operated with curative intent in 12 cases and for palliative reasons in 11. This was 4 and 2 for rectal cancer respectively.

Patients in group 2 underwent surgery with curative intent in 295 cases of colon cancer, and for palliation in 74. For rectal cancer this was 105 and 1 respectively.

Patients in group1 were significantly older than patients in group 2 ($p<0.001$), especially octogenarians were overrepresented (figure 1). However, in sub-analysis this was especially true for patients with colon cancer. The numbers in cases of rectal cancer did not reach statistical significance. But the number of patients who died was too low to reach definite conclusions.

Patients in group 1 with colon cancer also significantly had more often a higher stage compared with patients in group 2 ($p=0.03$) (table 1, figure 2). There was no difference in tumor localization.

Table 2 shows the Charlson co-morbidity score in both groups of patients. The mean Charlson co-morbidity score for patients with colon cancer in group 1 was 5.17 (SD 1.57, range 1-8), and for rectal cancer 4.83 (SD 2.32, range 2-7). Although there was a tendency towards a higher Charlson co-morbidity score in group 1 this was not significant (figure 2).

In patients with colon cancer of group 1 12 died as a direct consequence of surgical complications (acute surgery because of acute abdomen with peritonitis n = 3, post-operative bleeding requiring reoperation n = 3, anastomotic leakage requiring relaparotomy n = 5, abscess formation resulting in irreversible septic shock n =1). Eleven patients died due to complications induced by their pre-existing co-morbidity (cardiovascular n = 3, pulmonary complications n = 2, complications of pre-operative palliative chemotherapy n = 2, septicemia not related to the operation with multi organ failure n = 3, acute rupturing aneurysm n = 1). Causes of post-operative death in patients with rectal cancer were: anastomotic leakage n = 1, acute coronary problems n = 2, acute surgery because of perforation with peritonitis n = 2, and septicemia post radiation therapy.

DISCUSSION

The present study shows that 44% of patients who died in the post-operative period, died because of the direct technical complications of surgery. This is 2.2% of the total population of patients who underwent surgery. The remainder died because of the effects of existing co-morbidity. The five patients presenting with an acute perforation and peritonitis can be judged as indirect complication of surgery. In other words, without surgery these patients would have died anyway. Hence, the number dying of direct technical failure (anastomotic leakage, bleeding) is rather low. Of course, this is a somewhat biased conclusion. Without surgery these complications would not have occurred. On the other hand, patients in good clinical condition possibly have the strength to survive the complications due to

Table 1. age cohorts, localisation and Dukes classification in patients of groups 1 and 2 with colon and rectal cancer.

Colon cancer	Group 1	Group 2
Age (years)		
<60	2	77
61-70	4	104
71-80	6	127
>81	11	62
	p < 0.001	
Localisation		
sigmoid	8	169
descending colon	0	16
transvers colon	4	54
ascending colon	6	56
caecum	5	74
	p = ns	
Dukes classification		
Dukes A	2	45
Dukes B	3	141
Dukes C	6	90
Dukes D	10	82
unknown	2	11
	p = 0.03	
Rectal cancer		
age		
<60	2	22
61-70	0	39
71-80	1	27
>81	3	18
	p = ns	
Dukes classification		
Dukes A	0	17
Dukes B	1	43
Dukes C	2	37
Dukes D	1	8
Unknown	2	1
	p < 0.001	

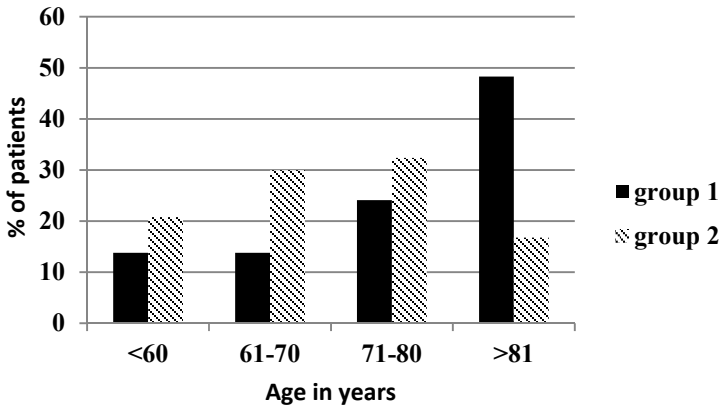

Figure 1. The age cohorts in colon and rectal cancer patients in both groups.

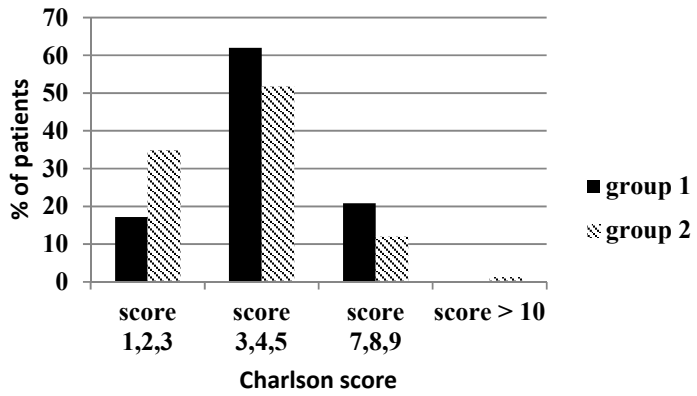

Figure 2. Charlson score in both groups of patients.

technical failure. Due to the application of post-operative prophylactic anticoagulant therapy no patient died because of thromboembolism.

In a large population based study in the Netherlands (25,591 patients undergoing colorectal resections in 92 hospitals), postoperative mortality rates ranged between 0% and 8.8%. Case-mix appeared an important cause of differences between hospitals. In addition, a large proportion of variation in mortality was due to chance.[10]

Functional health status predicts postoperative outcomes. A detailed preoperative evaluation, providing an optimization period before surgery if necessary, is mandatory.[11] Of course, the entire surgical team tries to minimize the risks of surgery in the individual patient. The introduction of laparoscopic techniques was a step forward in reducing mortality, particularly for the elderly.[12] If mortality occurs evaluation is needed in order to determine whether shortcomings in technique or care have occurred. Due to these post-operative evaluations surgical mortality decreased in the past decades.[13,14] But, patients still die without the surgical team being directly responsible.

The Charlson co-morbidity score is a well-known score for co-morbidity. Morris et al. showed that post-operative mortality increased in patients aged >80 years with a Charlson co-morbidity score ≥ 3, or with distant metastases, and in case of operative urgency.[13] It is to be expected that patients undergoing acute surgery because of an acute abdomen do die because of the critical clinical situation already present when surgery starts. The urgency character of the surgery does not allow proper rebalancing of the patients with respect to co-morbidity. This was also the case in the five patients in the present study presenting with an acute abdomen with peritonitis.

Surgical complications can be prevented by a proper technique and the severity of complications can be minimized by close post-operative surveillance in order to detect anastomotic leakage or bleeding early. Overall mortality rate is higher in patients after relaparotomy because of anastomotic leakage.[15] There appear to be several risk factors for this complication such as extensive tumor resection, emergency surgery, transverse colon resection, or subtotal colectomy.[16]

It is to be expected that patients who are healthy a have better outcome of anastomotic leakage compared with patients with cardiovascular or pulmonary problems. However, on the other hand a recent study showed that patients operated in hospitals with a higher reoperation rate did not have higher mortality rates.[17]

High age, especially above 80, is an important factor in post-operative mortality in cases of colorectal cancer. This is in accordance with the literature.[18] Factors that negatively influence results of surgery are diabetes and pre-existing cardiac pathology. The co-morbidity is an important factor in mortality because the majority of patients in this study died due to events related to their co-morbidity. This can be a case of bad luck, since there was no difference in co-morbidity with patients who survived the post-operative period.

The clinician has to make difficult decisions, especially in the older patient with colorectal cancer. One has to be aware of under treatment in healthy and fit older patients, while on the other hand overtreatment in the vulnerable or frail patient can lead to unacceptable postoperative outcomes with high mortality or persistent disability.[19] One has to keep in mind that the 1-year mortality after colorectal cancer surgery is high especially in older patients with a short life expectancy. A recent study in the Netherlands showed that 13% of patients died within the first postoperative year. Death was attributed to colorectal cancer in only 75% of patients.[20]

It is concluded that pre-existing co-morbidity is an important factor in post-operative mortality. The number of patients dying as a direct result of technical failure of the operation is rather low.

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THIRTY DAYS POST-OPERATIVE MORTALITY AFTER SURGERY FOR COLORECTAL CANCER

3

Part II

BENEFIT OF ADJUVANT CHEMOTHERAPY IN COLON CANCER

Chapter 4

HIGH RISK STAGE 2 AND STAGE 3 COLON CANCER, PREDICTORS OF RECURRENCE AND EFFECT OF ADJUVANT THERAPY IN A NON-SELECTED POPULATION

E.E. van Eeghen
S.D. Bakker
A. van Bochove
R.J.L.F. Loffeld

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ABSTRACT

Introduction

Patients with stage 3, and to a lesser extent stage 2, colon cancer often are treated with adjuvant chemotherapy.

Aim

Evaluation of prognostic factors and the benefit of adjuvant chemotherapy on recurrence free survival of patients in a non-selected population.

Patients and Methods

Evaluation of 243 consecutive patients diagnosed and treated at a single center for stage 2 and 3 colon cancer from 2002 to 2008. Adjuvant chemotherapy was applied in 66 patients. Data for recurrence free survival (RFS) were censored when death occurred before recurrence.

Results

Median overall survival (OS) was 5.84 years, median RFS was 5.37 years. N-stage, lymph node ratio (LNR), tumor location, and lymph vascular/peri-neural invasion were predictors of RFS in stage 2 and/or stage 3 disease ($p<0.05$). For stage 2 disease, patients treated with or without adjuvant therapy had a median RFS of 5.49 and 5.73 respectively (p=ns). For stage 3 disease, median RFS rates were 5.08 and 1.19 respectively (p=0.084). Overall relative dose intensity (RDI) of oxaliplatin based chemotherapy higher than median, was associated with increased RFS (p=0.045)

Conclusion

N-stage, LNR, tumor site, and lymph vascular/peri-neural invasion were predictors of recurrence. Adjuvant therapy did not significantly increase recurrence free survival, possibly due to a combination of insufficient power and a reduced effect size in the normal daily population compared to that of randomized controlled trials. This reduction is caused by the co-morbidity in patients. Relative dose intensity of oxaliplatin based therapy is associated with recurrence free survival.

INTRODUCTION

Colorectal cancer is the third most occurring cancer with an incidence of 80.0 per 100.000 in the year 2011 in the Netherlands. Although the prognosis of colon carcinoma has improved significantly over the past years[1], the mortality rate was still 30.5 per 100.000 deaths in 2011, which makes up for 11.8% of total cancer deaths. [2]

Curative therapy for colon cancer is largely determined by the lymph node status since positive lymph nodes provide an indication for adjuvant treatment with chemotherapy. [3, 4] Currently the combination of a 5-fluorouracil (5-FU) analogue and oxaliplatin is the treatment of choice. [5-7]

Trials treating patients with stage 2 disease with adjuvant therapy show mixed results. A number of studies comparing treatment with fluorouracil/leucovorin (5FU/LV) and observation showed little to no added benefit. [8-10] More recently, studies have been published showing benefit in treating patients with stage 2 disease with an increased risk of recurrence. [11-13] The presence of microsatellite instability (MSI) has been found to decrease the risk of recurrence and negate the effect of adjuvant chemotherapy on RFS in patients with stage 2 disease. [14, 15] The guideline published by the American Society of Clinical Oncology advises against the use of adjuvant therapy with the exception for patients with characteristics that increase risk of recurrence. [16] Patients with MSI and stage 2 colon cancer have no indication for adjuvant therapy.

Studies examining the influence of relative dose intensity (RDI) of adjuvant therapy on RFS in patients with colon cancer treated with 5FU/LV showed no effect of increased duration of therapy on recurrence free survival (RFS). [17, 18] However, the effect of RDI on recurrence free survival in patients treated with adjuvant oxaliplatin based therapy is still relatively unexplored. This information could prove valuable to clinicians and patients because the majority of patients treated with oxaliplatin face unacceptable toxicity resulting in dose reductions, delays, and early termination of treatment leading to a median RDI of 70-85%. [19-21]

Published randomized clinical trials poorly represent the day-to-day population treated by clinicians because of major selection and investigator bias. [22] Patients presenting with colon cancer often fulfill the exclusion criteria used in the trials. As such, clinicians have to base treatment decisions on guidelines representing at best, only part of their patient population. Previous observational studies show a survival benefit for adjuvant chemotherapy in elderly patients. However, due to their observational nature, these studies are also subject to significant selection bias, only partially corrected through propensity scoring. [23, 24]

Therefore, a study was done to evaluate which factors are associated with an increased risk of disease recurrence in patients with stage 2 and stage 3 colon cancer in a non-selected population seen in daily practice. In addition, the effect of adjuvant therapy, and its RDI, on RFS was studied. Sub-analyses for the RDI in different regimens were performed.

METHODS

A review of pathology, radiology, and endoscopy reports as well as other correspondence was done for all consecutive patients diagnosed and treated for colorectal cancer at the "Zaans Medisch Centrum", the community hospital of the Zaanstreek region in the Netherlands, from 2002 to 2008. Evaluation was done on 1-1-2014. In addition, the database of the hospital pharmacy was searched for all prescribed chemotherapy administered in the in- and out-patient clinic. Information on oral medication (Capecitabine) was obtained through chart review.

The relative dose intensity of the chemotherapy regimen was measured by averaging the RDI of each individual drug except for leucovorin. The RDI for each drug was calculated by multiplying the time index, the time allotted for the administered chemotherapy cycles divided by the duration of said cycles, and the dose index, the administered cumulative dose divided by the standard cumulative dose. (For the regimens used as reference, see appendix B.)[25, 26]

Relative dose intensity of chemotherapy was dichotomized by dividing patients into groups based on a RDI higher or lower than the median. Associations between RDI and RFS were determined for patients treated with regimens with and without oxaliplatin.

Recurrence free survival was calculated from date of surgery to date of radiological or histological signs of recurrence. Overall survival was measured from date of diagnosis to date of death.

Patient co-morbidity was measured using a Charlson age co-morbidity index. [27-29]

A full listing of exclusions and detailed description of study variables are noted in the appendices.

Recurrence free survival outcomes were tested using a Kaplan-Meier analysis. A Log-rank test was used to compare outcomes between groups. Univariable cox regression analysis was used to determine factors associated with increased recurrence free survival. Patients were censored at death if they had not experienced recurrence. Fisher's exact test and the independent sample t-test were used to evaluate differences between patient groups.

Statistical analyses were performed using IBM SPSS statistics software version 20.0 and Microsoft Office Excel 2010.

RESULTS

Data were studied of 621 consecutive patients with colorectal cancer treated at the Zaans Medisch Centrum. Three hundred seventy-eight patients were excluded for the present analysis (see appendix A). One hundred forty-three patients were diagnosed with rectal cancer, 149 patients presented with stage 0, 1, or 4 colon cancer, and 78 patients were excluded for other reasons. In this analysis 243 patients, 95 with stage 3 and 148 with stage 2, were included (Figure 1). Four patients with stage 2 disease could not be included in the cox regression analyses since they died almost immediately after surgery as a result of perioperative complications; hence, there was insufficient survival time.

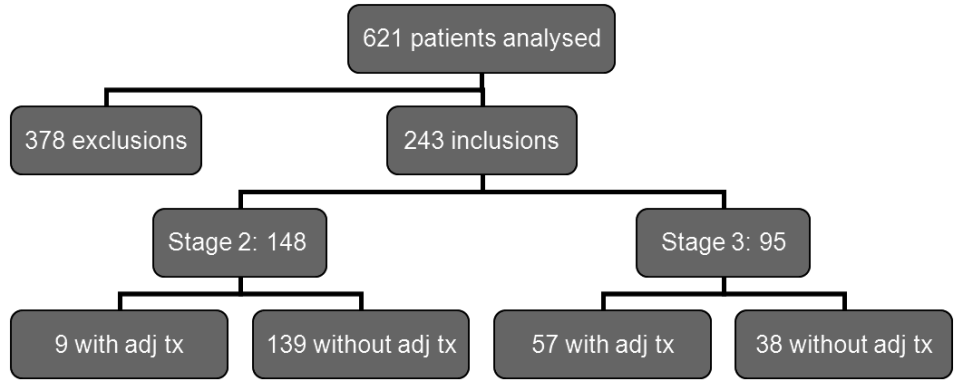

Figure 1. Included patients

All patients were followed for at least 5 years, or until death of any cause (range 0.0 – 11.8). Median follow up of patients was 5.84 years, interquartile range (IQR) 3.00 – 7.84. Disease recurrence occurred in 68 patients (28%): 29 patients (20%) with stage 2 disease and 39 patients (41%) with stage 3 disease (Table 1).

In patients with stage 2 disease the number of examined lymph nodes was inversely related to the risk of recurrence with a hazard ratio (HR) of 0.92 per node examined (Table 1).

The following variables in patients with stage 3 disease, were associated with recurrence free survival: N-stage (HR=0.32 for N1 versus N2), number of metastatic lymph nodes (HR 1.14 per positive node), LNR (HR 11.64 per point increase), tumor site (HR 0.47 for distal vs proximal tumors), and lymph vascular or peri-neural invasion (LVI or PNI) (HR=0.43 for patients without LVI/PNI).

Nine patients (6%) with stage 2 , and 57 patients (60%) with stage 3 disease received adjuvant chemotherapy consisting of either a 5-fluorouracil analogue, or folfox/capox (regimens consisting of either 5-fluorouracil and leucovorin or capecitabine in combination with oxaliplatin). There was no significant improvement in RFS when patients were treated with adjuvant chemotherapy. However, patients with stage 3 disease treated with adjuvant therapy did display a trend towards improvement with a 3.89 year longer median RFS.

With almost identical recurrence rates (p=ns), this trend is the result of the significantly longer overall survival in the stage 3 patients treated with chemotherapy ($p<0.001$). Patients with stage 3 disease without adjuvant treatment had significantly more co-morbidity according to the Charlson index ($p<0.001$). Therefore, they had a shorter life expectancy based on age and preexistent conditions. This reduces the relative risk of death from tumor progression. (Table 2 and figure 2).

Patients receiving adjuvant treatment with folfox or capox with a RDI higher than the median showed significant improvement of RFS (p=0.04). However, the sub analysis of the oxaliplatin dose intensity in patients treated with folfox or capox showed no significant improvement in RFS (Table 3 and figure 3).

Table 1. Patient characteristics and univariate cox regression analysis of effect on recurrence free survival.

		Stage 2	Cox HR for recurrence	95% CI	Stage 3	Cox HR for recurrence	95% CI	Total
Gender (%)	male	78 (53)			46 (48)			124 (51)
	female	70 (47)			49 (52)			119 (49)
Age, median (iqr)		73,5 (63,7 – 80,0)			69,3 (62,9 – 76,7)			72,2 (63,2 – 79,5)
T-stage (%)	3	123 (83)	0,64	0,27 – 1,49	66 (69)	0,53	0,27 – 1,01	189 (78)
	4	25 (17)			25 (26)			50 (21)
tumor site (%)	distal	62 (42)	1,1	0,52 – 2,33	48 (51)	0,47	0,24 – 0,91	110(45)
	proximal	77 (52)			44 (46)			121 (50)
Poor differentiation (%)		13 (9)	na		25 (26)	1,89	0,98 – 3,70	38 (16)
LVI or PNI (%)		15 (10)	1,89	0,72 – 5,00	17 (18)	2,33	1,12 – 4,76	32 (13)
N-stage (%)	0	148 (100)			0			148 (61)
	1	0			61 (64)	0,32	0,17 – 0,60	61 (25)
	2	0			34 (36)			34 (14)
Median # LN examined (iqr)*		13 (8 – 19)	0,92	0,87 – 0,98	13 (8 – 19)	0,97	0,93 – 1,01	13 (8 – 19)
Median # metastatic LN (iqr)*		0			2 (1 – 6)	1,14	1,08 – 1,21	0 (0 – 2)
Median LNR (iqr)*		0			0,29 (0,11 – 0,50)	11,64	4,10 – 32,99	0 (0 – 0,20)
Adjuvant therapy (%)		9 (6)	1,81	0,55 – 5,88	57 (60)	0,57	0,30 – 1,09	66 (27)
Recurrence (%)		29 (20)			39 (41)			68 (28)
Median OS (iqr)		6,38 (4,25 – 8,49)			5,00 (1,84 – 7,09)			5,84 (3.00 – 7,84)
median RFS (iqr)		5,72 (2,38 – 7,97)			3,04 (1,01 – 7,04)			5,37 (1,65 – 7,58)
total		148			95			243

HR = Hazard ratio; CI = confidence interval; iqr = interquartile range; LVI = lymphovascular invasion; PNI = peri-neural invasion; LN = lymph node; LNR = lymph node ratio; OS = overall survival; RFS = recurrence free survival
*For continuous variables, the hazard ratio is expressed per point increase.

Table 2. Effect of adjuvant therapy on (recurrence free) survival

		Stage 2 – adj Tx	Stage 2 + adj Tx	p	Stage 3 – adj Tx	Stage 3 + adj Tx	p
Number of patients		139	9		38	57	
Recurrence rate		0,19	0,33	0,379	0,42	0,4	1,000
median OS (iqr)		6,42 (4,25 – 8,59)	6,17 (2,08 – 7,42)	0,772	1,79 (0,60 – 6,07)	5,51 (4,06 – 7,47)	0,000
median RFS (iqr)		5,73 (2.76 – 8,11)	5,49 (1.33 – 7,31)	0,325	1,19 (0,36 – 5,94)	5,08 (2,12 – 7,40)	0,084
Median age (iqr)		75,3 (65,4 – 80,4)	61,0 (59,3 – 65,7)	0,002	78,7 (73,9 – 83,1)	63,5 (59,8 – 69,8)	0,000
Median Charlson index (iqr)		5 (3 – 6)	3 (2 – 4.5)	0,038	5 (4 – 6)	3 (3 – 4)	0,000
Cause of death (%)	Alive	87 (56)	5 (56)		8 (21)	32 (56)	
	Cancer	18 (13)	3 (33)		15 (40)	18 (32)	
	Treatment	3 (2)	1 (11)		8 (21)	0	
	Other	29 (21)	0		6 (16)	5 (9)	
	Unknown	11 (8)	0		1 (3)	2 (4)	

Adj Tx = adjuvant therapy; iqr = interquartile range; OS = overall survival; RFS = recurrence free survival.

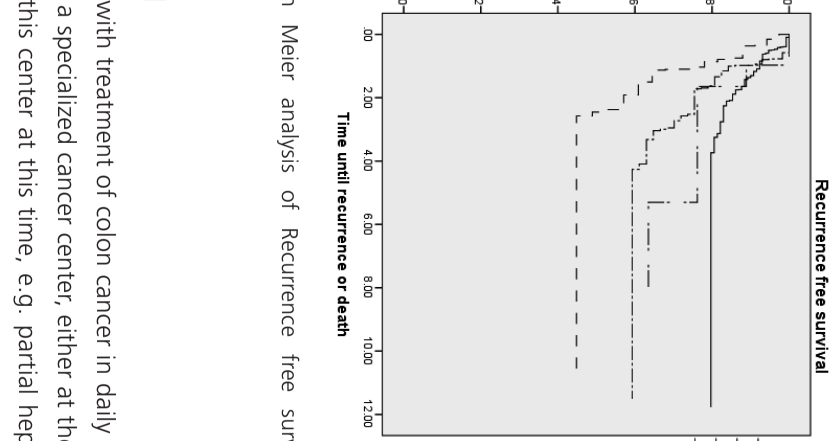

Figure 2. Kaplan Meier analysis of Recurrence free survival of patiens with or without adjuvant therapy

DISCUSSION

This study deals with treatment of colon cancer in daily practice. Eighteen patients (3%) were referred to a specialized cancer center, either at their own request or for treatment not available in this center at this time, e.g. partial hepatectomy. This introduces some inevitable selection bias. The long inclusion period of this cohort inadvertently causes differences in adjuvant treatment between patients diagnosed in 2002 versus 2008, the most important of which is the addition of oxaliplatin to adjuvant therapy in 2004. In this cohort 81% of patients treated with oxaliplatin based therapy received a folfox regimen. In many centers the preferred treatment is capox therapy. While capox is associated with a lower RDI, no significant difference in OS and RFS has been observed between treatments. [30]

Overall survival in this cohort is underestimated in patients not treated with adjuvant therapy compared to patients treated with adjuvant therapy and those observed in other cohorts due to the fact that patients dying of perioperative complications are included in this analysis. (See appendix D for characteristics of these patients). Since most of these patients are octogenarians and have a high Charlson index it seems reasonable to include them in the group not treated without adjuvant therapy as most would not qualify regardless.

This study shows an inverse correlation between the number of lymph nodes examined and the risk of recurrence in patients with stage 2 disease, and a trend towards increased risk of recurrence for patients with poorly differentiated tumors, LVI or PNI, and T4 status. Similar results were obtained for patients with stage 3 disease except for a significantly

Table 3. Influence of relative dose intensity on recurrence free survival.

		>median RDI	<= median RDI	p	Total
total	Number of pts	33	33		66
	median RDI (iqr)	0,92 (0,86 – 0,98)	0,65 (0,30 – 0,76)	0,000	0,83 (0,64 – 0,92)
	Recurrence rate	0,36	0,42	0,801	0,39
	Median RFS (iqr)	5,49 (2,12 – 7,91)	5,08 (1,52 – 6,83)	0,590	5,22 (1,71 – 7,39)
folfox/capox	Number of pts	20	22		42
	median RDI (iqr)	0,89 (0,84 – 0,95)	0,71 (0,44 – 0,76)	0,000	0,82 (0,70 – 0,87)
	Recurrence rate	0,1	0,36	0,071	0,24
	Median RFS (iqr)	6,94 (5,32 – 7,65)	5,11 (2,47 – 6,93)	0,045	5,51 (3,83 – 7,21)
oxaliplatin*	Number of pts	20	22		42
	median RDI (iqr)	0,88 (0,74 – 0,95)	0,50 (0,39 – 0,63)	0,000	0,67 (0,50 – 0,87)
	Recurrence rate	0,2	0,27	0,732	0,24
	Median RFS (iqr)	6,94 (3,40 – 7,65)	5,36 (3,83 – 6,93)	0,602	5,51 (3,83 – 7,21)
5FU	Number of pts	10	14		24
	median RDI (iqr)	1,00 (0,94 – 1,00)	0,55 (0,26 – 0,87)	0,000	0,87 (0,36 – 0,99)
	Recurrence rate	0,6	0,71	0,673	0,67
	Median RFS (iqr)	2,11 (1,11 – 10,21)	2,63 (1,25 – 5,50)	0,865	2,55 (1,20 – 9,47)

RDI = Relative dose intensity; pts = patients; iqr = interquartile range; RFS = recurrence free survival; 5FU = 5-fluorouracil (also includes capecitabine).
*Subanalysis of oxaliplatin RDI in patients treated with capox or folfox

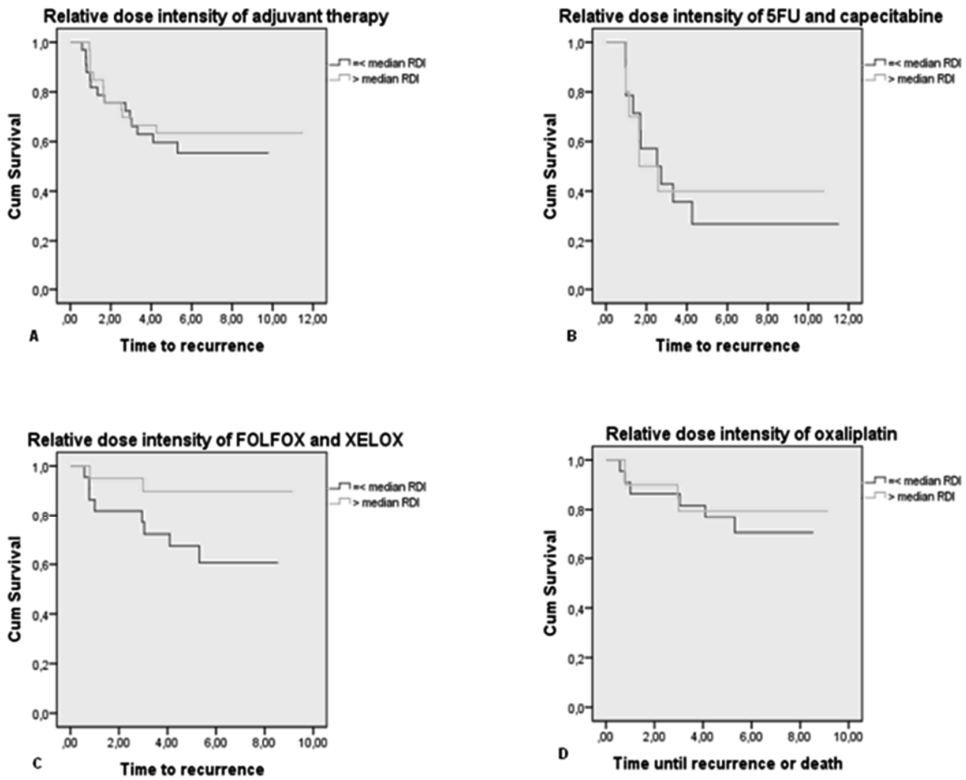

Figure 3a-d. Kaplan meier analyses of recurrence free survival based on relative dose intensity (RDI) of adjuvant chemotherapy.

increased risk of recurrence for proximal tumors and an increased LNR or N2 status. These results are in line with previous reports except for the association between tumor site and RFS. [12, 16, 31-36] As such, more evidence is needed to support this observation.

Several trials and meta-analyses have been performed to evaluate the added benefit of adjuvant chemotherapy in patients with stage 2 colon cancer. Many studies in the past have been insufficiently powered, and most of the evidence has come from pooled meta-analyses of trials including both patients with stage 2 and stage 3 disease. [8-11, 16, 37, 38] Currently, only patients with stage 2 disease who are perceived to be at an increased risk of recurrence and without microsatellite instability have an indication for adjuvant treatment. This reflects the treatment strategy in the Netherlands and might explain the observation of a, albeit not significant, higher recurrence rate in stage 2 patients treated with adjuvant therapy. Although this study contains only 9 patients with stage 2 disease treated with adjuvant therapy, this suggests that these patients are at increased risk of recurrence and might benefit from adjuvant treatment. This hypothesis is confirmed by previous findings from other studies [12, 13, 39-42] and supports the policies

outlined in the current Dutch and American guidelines for adjuvant treatment of colon cancer. [16, 43]

In this cohort, patients with stage 3 disease treated with adjuvant therapy experienced a non-significant increase in recurrence free survival compared to those treated with surgery alone. Recurrence rates were almost identical in patients treated with or without adjuvant chemotherapy. Since a significant survival benefit of adjuvant therapy in stage 3 disease has been demonstrated in multiple large randomized trials, the results observed here are somewhat disappointing. [3-5, 41] This could be due to a combination of lack of statistical power and a small effect size. This effect reduction can be explained by differences in characteristics between patients treated in daily life or in controlled clinical trials. Comparing the present population to that of the MOSAIC and the NO16968 trial, the median age in daily life is approximately 10 years higher. The median dose intensity of oxaliplatin was 11-13% lower in this cohort. The dose intensity of 5-FU single agent therapy was similar, although the MOSAIC study only describes a maximum dose index in 87% of patients. Furthermore, these trials have stricter exclusion criteria with regard to co-morbidity such as the NO16968 trial requiring an ECOG performance score of 1 or 0 and a life expectancy of at least five years. [6, 19] As such, one can conclude that the results from these trials might overestimate the benefit of adjuvant treatment and cannot be extrapolated to a majority of patients presenting with stage 3 disease in normal daily practice.

The similar recurrence rates observed in this cohort in patients treated with or without adjuvant chemotherapy indicate that increased co-morbidity and reduced overall survival decrease the efficacy of adjuvant therapy as they increase the risk of death from non-tumor related events. Thus a patient's survival benefit from adjuvant therapy is directly related to his or her life expectancy and should play an important role in the treatment decisions made by patient and clinician.

Regardless of the potential survival benefit, the toxicity and adverse events caused by adjuvant chemotherapy, especially oxaliplatin, result in significant patient morbidity. [20, 21] The notion that higher doses of chemotherapy, if tolerated, improve cancer related survival seems obvious, yet randomized controlled trials evaluating increased doses of chemotherapy show mixed results. [44-47] Chau et al. observed non-inferiority of a three month treatment schedule with 5FU/LV instead of six, and the GERCOR study showed no effect of longer treatment with 5FU/LV. [17, 18]

Although this retrospective analysis of the effect of dose intensity of chemotherapy on survival introduces bias based on co-morbidity and treatment strategy, most bias was removed by evaluating recurrence free survival in an adjuvant setting. A significant association between the RDI of oxaliplatin based therapy and recurrence free survival was observed. This did not translate into an effect of the isolated oxaliplatin dose on RFS, and as such seems to be mostly dependent on the RDI of 5-FU analogues. This could create an opportunity to lower the dose of oxaliplatin and reduce invalidating polyneuropathy

without significantly impacting outcomes. However, clinicians should proceed cautiously as these results do indicate an effect of dose intensity on outcomes in adjuvant treatment of colon cancer. Judgment should be withheld until results from a larger prospective study are presented.

In conclusion, this study presents evidence that the effect of adjuvant chemotherapy is overestimated in previously reported randomized clinical trials and does not reflect a non-selected population since co-morbidity is not factored into the equation. Furthermore, a high relative dose-intensity of oxaliplatin based adjuvant therapy is associated with improved recurrence free survival. Counseling the heterogeneous group of patients with stage 2 and 3 colon cancer about the benefits and downsides of (continuing) adjuvant therapy should be performed on a case by case basis.

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Chapter 5

EXTRAMURAL VENOUS INVASION AS PROGNOSTIC FACTOR OF RECURRENCE IN STAGE 1 AND 2 COLON CANCER

E.E. van Eeghen
M.J. Flens
M.M.R. Mulder
R.J.L.F. Loffeld

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ABSTRACT

Aim

Extramural venous invasion (EMVI) is a prognostic indicator in patients with colorectal cancer. However, its additional value in patients with stage 1 and 2 colorectal cancer is uncertain. In the present study the incidence of EMVI, and the hazard ratio for recurrence in patients with stage 1 and 2 colon cancer were studied.

Methods

184 patients treated for stage 1 and 2 colon cancer were included with a follow-up of at least 5 years. Chart review was performed and EMVI was assessed by two separate pathologists. EMVI was scored with additional caldesmon staining on the resection specimen. Primary outcomes were recurrence free survival (RFS) measured through cox regression analysis and prevalence of EMVI.

Results

There were 10 cases of EMVI and 3 cases of intramural venous invasion (IMVI) all occurring in patients stage 2 disease corresponding to a prevalence of 9%. Thirty one percent of patients with venous invasion experienced recurrence versus 14% in patients without, corresponding with a hazard ratio of 2.39 (p=0.11).

Conclusion

The present study demonstrates a trend towards an increased risk of recurrence in patients with stage 2 colon cancer with venous invasion. This warrants consideration of adjuvant chemotherapy despite the lack of lymph node metastases.

INTRODUCTION

Colon cancer is one of the most occurring malignancies in the Western world. Curative treatment is largely dictated by the TNM stage. A number of studies have demonstrated the benefit of adjuvant chemotherapy in stage 3 colon cancer. [1,2] This benefit is less clear in patients with stage 2 disease, and as such, clinicians have tried to confine treatment to patients with tumours with characteristics that present a high risk of recurrence. [3-6]

A previously underappreciated predictor of recurrence is (extramural) venous invasion ((EM)VI). Previous studies report hazard ratios of recurrence between 1.5 and 2.7 for patients with EMVI. [7-10] However, the inclusion criteria between studies differ, as does the reported prevalence of VI ranging from 23% to 28% in recent studies. Incidence of EMVI is correlated with disease stage being as low as 3% in stage 1 patients, up to 53% in patients with stage 4 disease in the study by Gibson et al. [7] Discrepancies in prevalence might also be the result of different staining techniques used in different studies, with some studies providing only haematoxylin / eosin (HE) staining. This method might lack sensitivity in detecting EMVI. [11-13] Roxburgh et al. conducted a study comparing 2 cohorts that had been analyzed through HE with or without additional elastic staining. Incidence of VI was 18% versus 58% in favour of elastic staining while 3-year survival remained similar in both VI positive groups (77% and 75%). [14] The present study is done in order to establish the prevalence of VI in stage 1 and 2 colon cancer using a caldesmon staining technique to increase sensitivity for intra- or extramural invasion. Secondly, the hazard ratio for recurrence of tumour in patients with stage 1 and 2 cancer, with and without VI was assessed.

METHODS

All patients with stage 1 and 2 colon cancer treated at the Zaans Medisch Centrum, the regional hospital in Zaanstreek region, in the Netherlands, between 2002 and 2008 were included. This was part of a much larger study on disease free and overall survival in patients with colorectal cancer. Analysis was done on 1-1-2014 providing at least 5 years of follow-up for all patients. An extensive chart review was conducted for all patients in order to retrieve tumour and patient characteristics. Except for venous invasion, all tumour characteristics are reported as described in the original pathology report. The Charlson age-comorbidity scale was used to assess patient comorbidity. [15,16]

Post-operatively the resection specimens were routinely fixed in formalin and embedded in paraffin wax. The routine 3 µm sections were stained with the standard haematoxylin / eosin stain. At time of the final analysis the patient was scored according to the TNM classification. For the present study, a tissue block with representative tumour was selected from the archive for immunohistochemical staining with caldesmon on the BOND III full automatic Leica stainer. The formalin fixed, paraffin wax-embedded sections were dewaxed. To enhance immunostaining, these sections were subjected to an epitope retrieval solution (high PH 9.0) for 20 minute at 100°C. Endogenous peroxidase

and non-specific binding were blocked before addition of the primary antibody. The slides were stained with the monoclonal antibody Caldesmon from Dako (Glostrup, Denmark), clone h-CD, 1:100. All sections were stained with the standardized 3,3-diaminobenzidine tetrahydrochloride (DAB) conjugate kit from Leica and counterstained with haematoxylin. The presence of tumour cells within venous structures beyond the bowel wall was assessed on all haematoxylin and eosin stained sections of the tumour, and with the additional use of caldesmon staining in representative and most suspected area of the tumour. The caldesmon staining is superior to the standard hematoxylin and eosin staining. Highlighting the vessels by caldesmon staining significantly increases the observed incidence of vascular invasion in colorectal cancer compared with hematoxylin and eosin alone. [17-19] Two experienced pathologists, MF and MM, scored the immunostaining results. They were blinded for patient outcomes. After independent assessment, cases coded as diagnostically discordant were discussed in a pathology panel discussion for consensus.

Log-rank and multivariable cox regression analyses were used to determine the hazard ratio of recurrence for patients with EMVI. In addition, a T4 tumour, lymph node yield, and poor histological differentiation was analyzed with respect to recurrence. Statistical analyses were performed using IBM SPSS 20.0. A p-value below 0.05 was considered statistically significant.

RESULTS

A total of 192 patients were treated for stage 1 and 2 colon cancer. From eight patients the original HE slides and/or the resection specimen were not available for reassessment, therefore these patients were excluded (appendix A). Table 1 shows the demographics and the localization of the tumour. Table 2 shows the characteristics of recurrence. Also Charlson index, differentiation grade and number of lymph nodes are noted.

In the remaining 184 patients, 10 (5.4%) cases of EMVI and 3 (1.6%) cases if IMVI were observed. EMVI was only diagnosed in patients with stage 2 disease. Three patients in the EMVI group experienced recurrent disease (30%), one in the IMVI group (33%), and 24 in the control group (patients without VI) (14%). Univariate cox-regression analyses yielded a hazard ratio of 2.39 for recurrence in the group with EMVI (p = 0.107) (figure 1a). Cox regression analysis for other tumour characteristics also known to cause an increased risk of recurrence free survival showed no significant outcomes. Hazard ratio's for recurrence for T4 tumour's was 2.02 (figure 1b). Every (negative) lymph node examined yielded a 4.0% reduction in risk of recurrence. Patients with LVI/PNI had a hazard ratio for recurrence of 2.21 (figure 1c). Proximal tumours were associated with a hazard ratio for recurrence of 0.93 (figure 1d). No analysis was performed for the differentiation grade as none of the 13 patients with poorly differentiated tumours experienced recurrence.

Table 1. Patient characteristics

		EMVI		IMVI		no EMVI	
Number of patients		10		3		171	
Gender	Male	5	50%	0	0%	94	55%
	Female	5	50%	3	100%	77	45%
Age*		78	(56 - 85)	70		73	(66 - 80)
Charlson age index*		5.5	(2.75 - 7.25)	5		5	(3 - 6)
T-stage	1	0	0%	0	0%	10	6%
	2	0	0%	0	0%	33	19%
	3	9	90%	3	100%	106	62%
	4	1	10%	0	0%	22	13%
Differentiation	poor	0	0%	0	0%	13	8%
	Well	10	100%	3	100%	151	92%
Adjuvant Treatment		0	0%	0	0%	8	5%
LVI/PNI		2	80%	0	0%	14	8%
# examined lymph nodes*		8.5	(5.5 - 15.25)	19		13	(8 - 18)
Tumor location	Distal	6	60%	0	0%	77	45%
	Proximal	4	40%	3	100%	86	50%
	Synchronous	0	0%	0	0%	8	5%
Recurrence		3	30%	1	33%	24	14%
Overall survival*		5.96	1.21 - 9.24	5.58		6.75	5.09 - 8.59
Cause of death	Alive	4	40%	0	0%	108	63%
	Tumor	2	20%	1	33%	15	9%
	Complication of treatment	0	0%	0	0%	6	4%
	Other	3	30%	2	67%	31	18%
	Unknown	1	10%	0	0%	11	6%

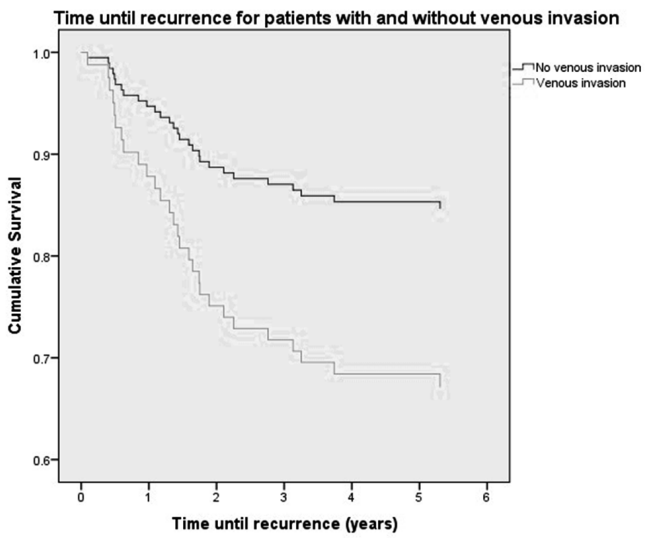
EMVI: Extramural invasion, IMVI: intramural invasion, LVI/PNI: lymphovascular invasion/perineural invasion.
*median and (interquartile range)
No interquartile ranges were reported for the EMVI group due to the small number of patients.

Table 2. Characteristics associated with recurrence.

	Cox-hazard ratio	95% Confidence Interval
EM-+IMVI	2.39	0.83 - 6.89
T4	2.02	0.87 - 4.69
Differentiation	no events in patients with poor differentiation	
LVI/PNI	2.21	0.85 - 5.75
# examined lymph nodes*	0.96	0.92 - 1.01
tumor location (distal is reference)	0.93	0.45 - 1.9

EM-+IMVI: extramural- and intramural venous invasion, LVI/PNI: lymphovascular/perineural invasion. Tumor location is divided in tumor distal and proximal to the flexura lienalis. Hazard ratio's are determined through univariate cox regression analysis.
*Hazard ratio's are reported for each additional lymph node examined.

1a



1b

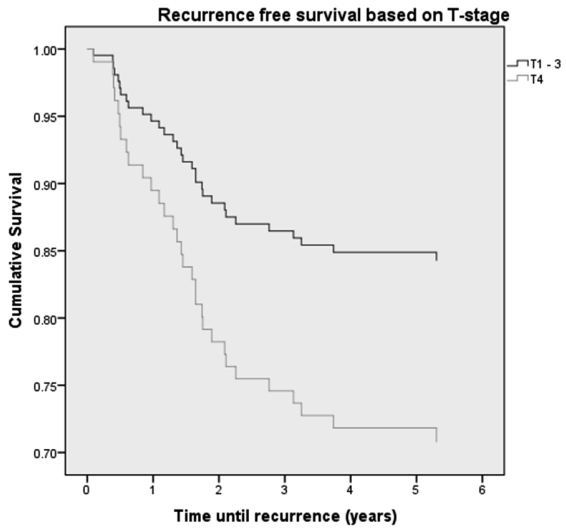
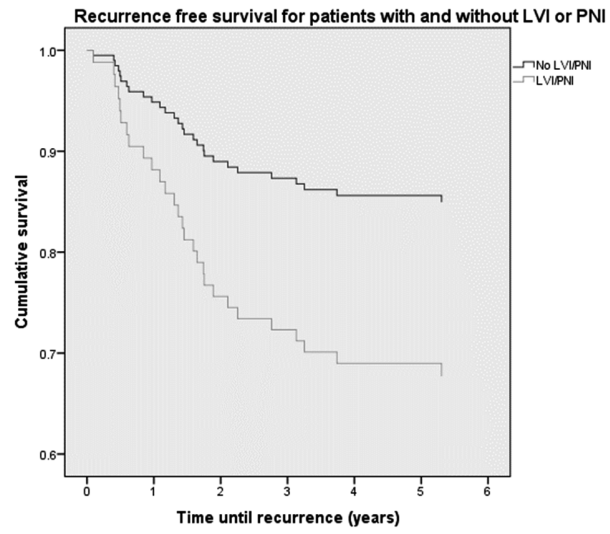


Figure 1a-d. Kaplan-meyer plots reporting the association of tumor characteristics and recurrence free survival. Patients were censored if death occurred before recurrence.
1a: IM-+EMVI, 1b: T4 tumor, 1c: LVI/PNI, 1d: distal vs proximal tumors.
LVI/PNI: Lymphovascular or perineural invasion.

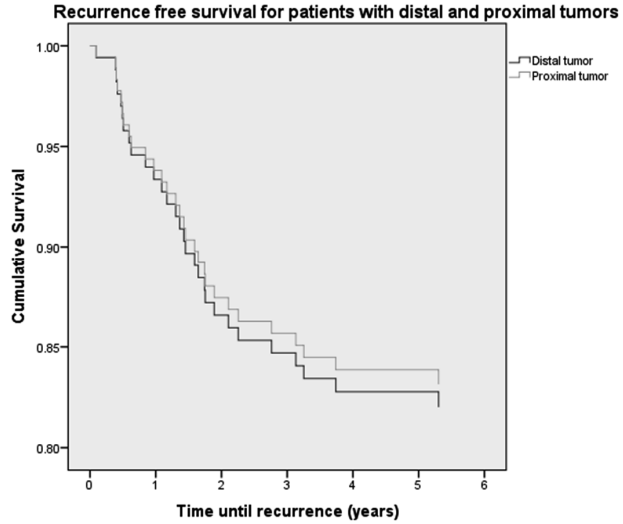
DISCUSSION

This study adds to evidence that venous invasion is a predictor of recurrence in colon cancer. This study is unique since only patients with stage 1 and 2 colon cancer are included. Most studies presented in the literature report on disease free survival and recurrence

1c



1d



free survival while only a minority of the studied patients actually have a follow-up after treatment of five years. A trend was found with respect to recurrence in patients with VI in stage 2 colon cancer. A possible drawback could be the relatively low number of patients. The recurrence rate was an alarming 31% in patients with VI, compared to 10-20% in all patients with stage 2 disease. [3,4] The hazard ratio of recurrence of 2.39 was similar to that reported by other studies. Although in most studies, hazard ratios included patients with (locally) advanced disease. Gibson et al. only found a significant increase of recurrence in patients with stage 3 disease. [7] While several other studies did find an association between (recurrence free) survival and venous invasion in patients with stage

2 disease. [8,10,20,21] Accurately determining risk of recurrence is most important in patients with stage 2 disease as adjuvant chemotherapy is not usually indicated, but can be added to improve prognosis in high risk patients.

Routine haematoxylin / eosin staining is not sufficient to detect extramural vascular invasion. More specific stains have to be used. [22] The caldesmon stain is by far the most accurate. After analysis by two GI specialized pathologists, prevalence of venous invasion appeared to be rather low with 0% and 9% in patients with stage 1 and 2 disease respectively. Detection rates of VI in patients with stage 2 disease range from 10 – 34% in previous studies. [7,8,10,20,22] Because of the influence of (EM)VI on recurrence risk, the Royal College of Pathologists has added VI to the "core data items" and stipulates a minimum overall detection rate of VI of 30% as audit criterion recommending the use of elastic staining and the evaluation of at least 2 blocks, especially if the detection rates are not matched. [24] However, a Canadian survey shows that these detection rates are currently far from being met. [19] Secondly, with the introduction of colorectal cancer screening the percentage of patients presenting with local disease increases, thus the incidence of EMVI will decline. [25] Conversely, this increase in local disease further underlines the need for proper risk stratification of these patients.

In conclusion, this study adds to previous evidence demonstrating an increased risk of recurrence in patients with stage 2 colon cancer with venous invasion. In this study, thirty one percent of these high risk patients experienced recurrence. Prevalence of EMVI varies between studies and pathologists, more precise guidelines with regard to the staining and number of evaluated blocks should be formulated. This is especially important for patients with stage 2 disease, as the high recurrence rate for EMVI positive tumours warrants consideration for adjuvant chemotherapy despite the absence of lymph node metastases. One should also take into account the presence of additional risk factors for recurrence (eg. a T4 tumour).

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Part III

NEOADJUVANT TREATMENT AND STAGING OF RECTAL CANCER

Chapter 6

OUTCOME OF RECTAL CANCER AFTER RADIOTHERAPY WITH A LONG OR SHORT WAITING PERIOD BEFORE SURGERY, A DESCRIPTIVE CLINICAL STUDY

E.E. van Eeghen
F.C. den boer
S.D. Bakker
R.J.L.F. Loffeld

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ABSTRACT

Background

Radiotherapy and surgery have shown to improve local control and survival in rectal cancer. There are two applied schedules; radiotherapy with a long or short waiting period before surgery. The effect on survival and recurrence of both schedules was studied.

Methods

All consecutive patients with rectal cancer in the period 2002 – 2008 were included. Data were gathered on survival, tumour stage, co-morbidity score, and cause of death. The patients were divided in three groups: group 1 patients undergoing surgery without neo-adjuvant radiotherapy; group 2 patients undergoing radiotherapy followed by immediate surgery; and group 3 patients treated with (chemo) radiotherapy followed by a longer waiting period.

Results

113 patients with rectal cancer underwent surgery. Twenty two patients in group 1, 71 patients in group 2, and 20 in group 3. There was no difference in gender, time to recurrence, co-morbidity score, or causes of death. Fifty percent of patients died due to non-cancer related causes. Mean age in patients of group 3 was significantly lower than in groups 1 and 2 ($p = 0.02$). There was a trend towards a lower tumour stage in the patients of group 3. Overall five year survival was 32% in group 1, 48% in group 2, and 35% in group 3.

Conclusion

Neo-adjuvant radiotherapy seems to be of benefit in daily practice in patients with rectal cancer. A longer waiting period results in down-staging. Clinicians have to be aware that many patients will die due to other causes than those related to the rectal cancer.

INTRODUCTION

Rectal cancer is one of the most prevalent cancers in the gastrointestinal tract.[1] The only curative treatment option is surgery. In the past local recurrences were a major problem. (Neo)-adjuvant radiotherapy in combination with conventional surgery, has shown to improve local control and survival. The Dutch Total Mesorectal Excision (TME) trial investigated the value of radiotherapy in combination with surgery. The local recurrence risk almost halved after six years of follow-up. However, an effect on overall survival could not be demonstrated.[2-4]

There are two frequently applied schedules of neo-adjuvant (chemo)radiation. The first one is radiotherapy 5 times 5 Gy followed by immediate surgery, the second one is radiotherapy in combination with chemotherapy followed by a longer waiting period before the actual surgical resection. According to the literature there is no difference in outcome with respect to overall survival, recurrence free survival and local recurrences between both schedules.[5,6]

However, patients reported in the literature are not representative of the population seen in daily practice. In trials strict inclusion and exclusion criteria are used. In the studies by Peeters and Sebag-Montefiore median ages were comparable to the one in a cohort in our clinic.[7] However, 99% of patients in the study by Sebag-Montefiore had a WHO performance score of 1 or higher indicating that a group of patients with more co-morbidity has been excluded. Unfortunately functional status of patients in this cohort has not been documented.[3,4]

In daily practice doctors are confronted with patients fulfilling many or all exclusion criteria applied in clinical trials. Hence, data from the literature cannot always be extrapolated to daily practice. For this reason, a study was done in usual daily practice in a group of consecutive patients with rectal cancer in order to gather data on survival and recurrences and to correlate these to the kind of radiotherapy that was given.

PATIENTS AND METHODS

All consecutive patients diagnosed with rectal cancer in the period 2002 – 2008 were included in the present study. This period was chosen in order to obtain adequate follow-up data of all patients. An extensive search was done of clinical records in order to evaluate the clinical course of the patients.

For all patients, treatment was determined, in addition, data were gathered on survival, stage of the tumour, co-morbidity according to the well-known Charlson age-comorbidity score, and cause of death. It was determined whether death was the result of the rectal cancer itself, the complication of the treatment, or not related to rectal cancer at all (death due to co-morbidity, this is non-cancer related causes). Evaluation was done in January 2014. Hence, follow-up was longer than 5 years in all patients.

The patients were divided in three groups: group 1 patients undergoing surgery without neo-adjuvant radiotherapy; group 2 patients undergoing 5 x 5 Gy radiotherapy

followed by immediate surgery (short course, within 4 weeks after radiation); and group 3 patients treated with (chemo) radiotherapy followed by a longer waiting period (long course) before actual surgery. The decision to choose for the short or the long course was made in a multi-disciplinary meeting and was based on clinical judgment and imaging of tumour extension, N-stage and the intention to downsize the tumour in the long course. Patients who did not undergo surgery, obviously, were excluded0

Statistical analysis was done with chi-square test for contingency tables and t-test. A value below 0.05 was considered significant.

RESULTS

In the period of 7 years a total of 143 patients was diagnosed and treated for rectal cancer. Of these, 113 underwent surgery. This is the group analyzed in this study. Twenty two patients (12 men, 10 women) underwent surgery without neo-adjuvant radiotherapy (group 1). Ninety one patients (55 men, 36 women) were treated with neo-adjuvant radiotherapy; 71 patients in the short course (group 2), and 20 in the long course s chedule (group 3).

Table 1 shows the results in the three groups of patients. There was no difference in gender. Mean age in patients of group 3 was significantly lower than in groups 1 and 2 (p = 0.02). There was no significant difference in cause of death between the three groups. Recurrence of disease occurred in all three groups without any difference. Figure shows the recurrence free period graphically. There was no significant difference in time to recurrence. There was a trend towards a lower tumour stage in the patients of group 3, implying successful down-staging of the tumour. There was no difference in co-morbidity score. Figure 2 shows the five year survival. There was no significant difference between the three groups. Overall five year survival was 32% in group 1, 48% in group 2, and 35% in group 3.

DISCUSSION

Treatment decisions have to be made by clinicians relying on data from the literature that cannot always be strictly applied to their patients. Hence, in daily practice, sometimes decisions have to be made that contradict the guidelines from the literature. So, our study population represents daily practice and the outcome data are comparable to those of selected patients included in randomized controlled trials. All patients treated for rectal cancer, in the time period of this study, were discussed in a multi-disciplinary meeting with oncologists, gastroenterologists, radiologists, radiotherapists and surgeons. On the basis of the clinical and radiological presentation, and data from the literature, a therapeutic regimen was chosen. In the study period neo-adjuvant radiotherapy was applied in all patients with a T3 stage and judged fit enough to undergo the treatment. In the final years of the study period chemo-radiation was also applied in some patients on basis of the N-stage. In that aspect this study presents unique data, since there is also a group

Table 1. demographics, tumour stage, survival, Charlson co-morbidity score and causes of death in the three groups of patients.
Group 1: no neo-adjuvant treatment; group 2: 5 x 5 Gy followed by surgery within four weeks; and group 3: neo-adjuvant therapy followed by long interval until surgery.

	Group 1	group 2	group 3
Number	22	71	20
Men	12 P = ns	43	12
Mean age (SD)	75.5(10.5) P = <0.001	69.8(9.7)	63.5 (7.8)
Deceased	15 P = ns	37	13
Cause of death			
Tumour related	5(33.3%)	17(45.9%)	5(38.5%)
Therapy related	05(13.5%)	2(15.3%)	
Not related to cancer	10(66.7%) P = ns	15(40.6%)	6(46.2%)
Recurrence	6(27%) P = ns	19(27%)	10(50%)
Time to recurrence			
Mean	(SD)1.83(0.89)	1.46(1.19)	2.11(1.73)
Range	0.8-2.9 P = ns	0-4.5	0.1-5.6
Tumour stage (as determined in the resection specimen)			
1	6(27.2)	10(14)	0
2	8(36.4%)	25(35.2%)	12(60%)
3	6(27.2%)	29(40.8%)	3(15%)
4	1(4.6%)	5(7%)	3(15%)
Unknown	1(4.6%)	2(3%)	2(10%)
Charlson score	5(2) P = ns	4.13(1.73)	3.95(2.06)

of patients not been treated with neo-adjuvant therapy. The five year survival was much lower than reported in the literature. Presence of co-morbidity is an important factor in mortality. These patients usually do not participate in clinical trials, simply because of their co-morbidity. There was no difference in the three groups with respect to overall survival. Also there was no difference with respect to recurrent disease. An important observation is the fact that many patients do not die because of cancer but because of

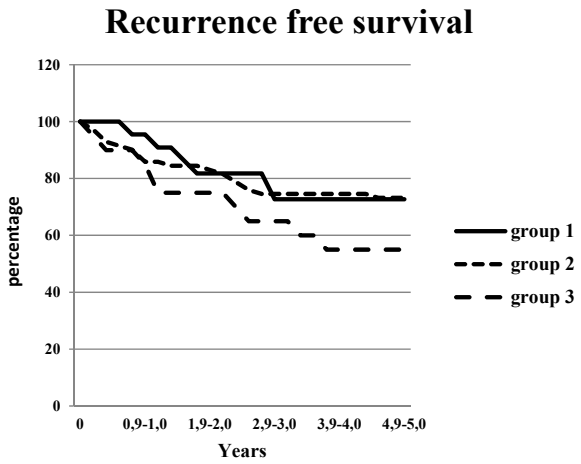

Figure 1. Recurrence free period in the three groups

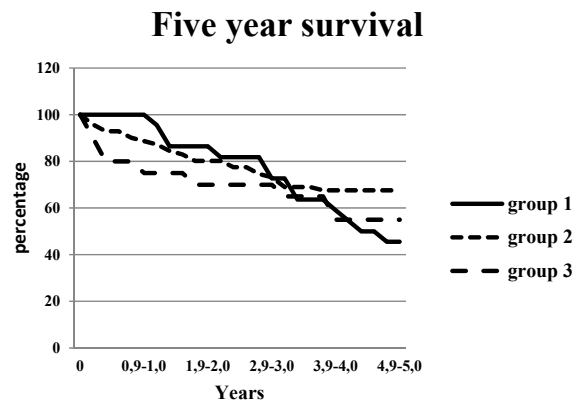

Figure 2. overall survival in all patients

non-cancer related causes. This reduces the effect of treatment on overall survival. This is important when discussing survival after treatment of cancer. The majority of the patients in our study was older with a limited life expectancy. The patients in the three groups are comparable with respect to gender and co-morbidity score.

At first glance, there is no benefit between surgery with or without neo-adjuvant radiotherapy. Indeed, survival and recurrence rate was the same for all three groups. However, these results can also be interpreted differently. Patients receiving neo-adjuvant radiotherapy had a higher clinical stage at presentation. Despite this the results of treatment were the same as in patients with a low stage of disease, possibly because of the effect of radiotherapy. It could be speculated that if the patients in groups 2 and 3 did not undergo neo-adjuvant therapy the survival would have been worse.

Short-term 5x5 Gy radiotherapy has become a popular preoperative treatment for patients with resectable rectal cancer in the Netherlands. An older study clearly demonstrated improved overall survival with radiotherapy. This study used radiotherapy followed by surgery within one week. The overall five-year survival rate was 58 percent in the radiotherapy-plus-surgery group and 48 percent in the surgery-alone group (P=0.004).[8,9] The intention to down stage the tumour was the argument for a longer waiting period after radiation. According to a meta-analysis, short course radiotherapy with immediate surgery is as effective as long-course chemo-radiotherapy with delayed surgery for the treatment of rectal cancer in terms of overall survival, disease free survival, local recurrence rate, and distant metastases.[5,6] Down-staging the tumour is the purpose of radiotherapy. Foster et al. did a literature review. They found limited evidence to support decisions regarding when to resect rectal cancer following chemo-radiotherapy. There may be benefits in prolonging the interval between chemo-radiotherapy and surgery beyond the 6 to 8 weeks that is commonly practiced.[10] However, there are also data which do not show any down-staging. Sirohi et al. did a retrospective analysis in 110 patients and concluded that timing of surgery, a longer time interval, did not influence pathological response.[11] In a study by Perez et al. it was shown that increased uptake of FDG during PET-scan was a sign of absence of down-staging.[12] In the present study there was a trend towards successful down-staging after a longer waiting period. This did not reach statistical significance probably due to the low number of patients in this group.

The final conclusion of the present study is that neo-adjuvant radiotherapy seems to be of benefit in daily practice in selected patients with rectal cancer. Co-morbidity score is not of influence on the outcome. A longer waiting period after radiation therapy results in successful down-staging as expressed by the lower Dukes stage of the resected specimen. In addition, clinicians have to be aware that many patients will die due to other causes than those related to the rectal cancer itself, irrespective of the outcome of rectal cancer treatment.

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Chapter 7

TUMOR STAGE IN PATIENTS OPERATED FOR RECTAL CANCER: A COMPARISON OF THE PRE-OPERATIVE MR AND THE RESECTION SPECIMEN, WITH SPECIFIC ATTENTION TO THE EFFECT OF NEO-ADJUVANT RADIOTHERAPY

E.E. van Eeghen
S.D. Bakker
G. Fransen
M.J. Flens
R.J.L.F. Loffeld

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ABSTRACT

Introduction

Post-operative stage of rectal cancer often differs from the pre-operative staging. Is this an effect of down-staging as a result of neo-adjuvant therapy or failure of MR?

Aim

Evaluate the preoperative TN stage with MR and the postoperative stage with histology.

Patients and method

Patients diagnosed with rectal cancer (2002 – 2015) and a pre-operative MR were included. A chart review was done. Pathology reports were evaluated for the post-operative tumor stage. Down staging was defined as a lower disease stage in the resection specimen compared with the pre-operative MR. Upgrading ("progression") was defined as a higher disease stage in the resection specimen.

Results

From 176 out of 231 operated patients a pre-operative MR was available for evaluation. 142 patients (80.7%) underwent neo-adjuvant treatment; the remainder 19.3% underwent immediate surgery. Neo-adjuvant therapy resulted in significant down staging. However, almost 14% of patients had a higher TN stage as determined by the pre-operative MR. In patients who underwent immediate surgery the percentage with "progression" was 30%. The number of patients with stage 1 and 2 were higher in the group not treated with neo-adjuvant therapy. There was no significant difference in tumor stage as determined by histological examination of the resection specimen.

Conclusion

The diagnostic accuracy of the MR is not perfect. Underestimation as well as overestimation of the tumor occurred both in the patients treated with radiotherapy as well as those who underwent immediate operation. As such, MR results should be interpreted with caution when devising a treatment strategy.

INTRODUCTION

Colorectal cancer is one of the most occurring malignancies in the Western world.[1,2] Surgery is the only curative option, with risk of (local) recurrence being a large concern as it is responsible for significant morbidity and mortality.[3]

Patients presenting with rectal cancer undergo radiologic staging at the time of diagnosis to determine the extent of disease in order to decide on optimal treatment. The tumor/ node/ metastasis (TNM) system is used to describe numerically the anatomical extent of cancer.[4] Magnetic resonance tomography (MR) and, to a lesser extent, endorectal ultrasound in addition to endoscopy are used to evaluate the extent of the primary tumor in relation to the mesorectal fascia, and the invasion of surrounding lymph nodes pre-operatively.[5,6] These examinations help determine the optimal surgical approach, and the need for neo-adjuvant radiotherapy and chemotherapy (CRT).

In daily practice it appeared that the post-operative tumor stage, as determined by the histological examination of the resection specimen (the only true gold standard), can differ from the pre-operative staging. Is this is an effect of down-staging as a result of CRT or simply a misinterpretation of MR?

A study by Akasu et al. shows the MR to be highly accurate in patients undergoing resection without neo-adjuvant CRT for predicting T-stage, though only moderately effective in detecting lymph node metastases.[6] Down staging could result in the need for less invasive surgery and thus reduced peri-operative morbidity without harming prognosis.[7,8] However, the role of restaging through MR after CRT is controversial as the diagnostic accuracy is low, presumably due to reactive changes after therapy that are hard to distinguish from residual tumor.[9]

A study was done in normal daily practice, in patients with rectal cancer who underwent curative surgery. The purpose was evaluate the preoperative TN stage with MR and the postoperative stage with the histological investigation of the resection specimen. The findings were correlated with the application of neo-adjuvant therapy.

PATIENTS AND METHOD

All consecutive patients diagnosed with rectal cancer in the period 2002 – 2015 in the Zaans Medical Centre, the community hospital of the Zaanstreek region in the Netherlands, were included. An extensive chart review was done in order to obtain data on pre-operative work-up, neo-adjuvant treatment, surgery and post-operative examination of the resection specimen.

Only patients in whom a pre-operative MR was done were included in the present study. In the first years of the study period the circumferential margin was not described in the routine MR. For this reason the circumferential margin was not scored in the present study. Pathology reports were evaluated for the correct post-operative tumor stage. Down staging was defined as a lower disease stage and lower T- and/ or N-stage in the resection specimen compared with the pre-operative MR. Upgrading ("progression") was defined

as a higher disease stage and T- and/or N-stage in the resection specimen as determined by the pre-operative MR.

Statistical analysis was done with chi-square testing for contingency tables. A value below 0.05 was considered statistical significant.

The study was approved by the ethical committee of the Zaans Medisch Centrum.

RESULTS

In the study period a total of 343 patients were diagnosed with rectal cancer. Of these 67.6% underwent surgical resection. The remainder already had metastatic disease (stage 4) rendering surgery futile or were in a very poor clinical condition due to co-morbidity.

From 176 patients (75.8%) a pre-operative MR was available for evaluation. One hundred forty two patients (80.7%) underwent neo-adjuvant treatment, the remainder 19.3% underwent immediate surgery.

Neo-adjuvant therapy resulted in significant down staging as shown in table 1. However, despite the neo-adjuvant treatment almost 14% of patients had a higher TN stage as determined by the pre-operative MR. In patients who underwent surgery without neo-adjuvant therapy the percentage with "progression" was almost 30%. Down staging also occurred, however, only in three patients. Table 2 shows the different tumor stages

Table 1. disease stage according to pre-operative MR and histological investigation of the resection specimen.

Disease stage	Neo-adjuvant therapy	No neo-adjuvant therapy
MR = histology	42(44.7%)	14(58.3%)
MR > histology	39(41.5%)	3(12.5%)
MR < histology	13(13.7%)	7(29.2%)
	P = 0.01	

Table 2. disease stage according to MR and histology

Disease stage by MR and histology	Neo-adjuvant therapy	no neo-adjuvant therapy
MR stage		
MR stage 1	10(10.6%)	8(34.8%)
MR stage 2	23(24.5%)	12(52.2%)
Histology stage		
Histology stage 1	27(31%)	6(28.6%)
Histology stage 2	20(23%)	7(33.3%)
Histology stage 3	40(46%)	8(38.1%)
	P = ns	

in both groups of patients. As to be expected the number of patients with stage 1 and 2 were higher in the group not treated with neo-adjuvant therapy. There was no significant difference in definite tumor stage as determined by histological examination of the resection specimen.

Table 3 shows the results of comparison of pre-operative MR-staging and histological examination of the resection specimen. In 7 patients no viable tumor was present anymore in the surgical resection specimen after neo-adjuvant therapy. This was not the case in any one of the patients who underwent immediate surgery.

DISCUSSION

The work-up and treatment of rectal cancer has changed in the past decennium. Especially since the results of neo-adjuvant radiotherapy on recurrence and overall survival has been published [10]. Short term radiotherapy followed by resection is the mainstay of treatment. Whether a long or short waiting period after radiotherapy is necessary still is a matter of debate.[11,12] In the cohort diagnosed and treated in the Zaans Medisch Centrum a longer waiting period results in a better outcome.[13]

The present study is part of a much larger study on disease free survival, recurrence, and co-morbidity in patients with colorectal cancer.[14] The study population of patients with rectal cancer was extended with all patients diagnosed in the period 2009 – 2015. The majority of cases were discussed in a multi-disciplinary meeting of gastroenterologists, oncologists, surgeons, radiotherapists, radiologists, and pathologists. On basis of all available data the best treatment for the patient was chosen.

In the present study a number of patients did not receive neo-adjuvant radiotherapy, mostly due to the low tumor stage as assessed by the pre-operative MR. This presented the unique opportunity to study the pre-operative staging using MR in comparison with the definite resection specimen as gold standard.

Table 3. Results of pre-operative MR staging and histological examination of the resection specimen.

MR and Histology	Neo-adjuvant therapy	no neo-adjuvant therapy
T-status		
MR = histology	46(49.5%)	14(60.9%)
MR > histology	42(45.2%)	5(21.7%)
MR < histology	5(5.3%)	4(17.4%)
	P = 0.04	
N-status		
MR = histology	42(44.7%)	16(69.69%)
MR > histology	38(40.42%)	0
MR < histology	14(14.9%)	7 (30.4%)

MR > histology indicates down staging. MR < histology means: MR staging was lower than definite histological investigation.

There are several MR parameters required to optimize staging of rectal cancer. Important aspects are the circumferential resection margin, extramural vascular invasion, and lymphnodes.[15] In the present study the T and N stage was specifically noted. In the literature several studies have been published on the accuracy of pre-operative MR of the pelvic region. Overestimation, as well as underestimation of the TN stage have been reported. Halefoglu et al. report a diagnostic accuracy of 75% for T-stage and 62.4% for N stage. Moriones et al. report similar findings with an accuracy of 72% and 60% respectively.[16,17]

The goal of radiotherapy is down-staging and down-sizing the tumor. It allows for less extensive surgical resections and reduces the risk of local recurrence.[18-20] Yang et al. studied the significance of tumor volume and its change after concurrent CRT. The TN stage was down staged in 60% of patients, including 23.3% with complete responses. All tumors showed volume reduction.[21] As to be hoped and expected, the present study showed significant down staging of neo-adjuvant therapy. However, MR underestimated the T/N stage in a number of patients. The final histological examination did not show a difference between both groups of patients. This indirectly indicates important down staging.

In conclusion, the present study shows significant down staging as a result of neo-adjuvant therapy. However, a higher tumor stage was present in 13.8% of patients despite the neo-adjuvant radiotherapy. Given the normal biological character of cancer this can be expected. Tumors grow and spread towards lymph nodes. The diagnostic accuracy of the MR is not perfect. This could be cause for concern as earlier reports of diagnostic accuracy could be an overestimation of daily practice due to the expertise of participating radiologists. Underestimation as well as overestimation of the tumor occurred both in the patients treated with radiotherapy as well as those who underwent immediate operation. As such, MR results should be interpreted with caution when devising a treatment strategy. Nevertheless, the beneficial effect of radiotherapy is irrefutable with some patients even showing complete pathologic response.

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Chapter 8

SUMMARY AND DISCUSSION

SUMMARY

Colorectal cancer is the second leading cause of cancer related death behind lung cancer. Large improvements have been made in the treatment of colon cancer in the past twenty years with more effective but also more radical treatments becoming available. With the increasing life expectancy in the Western world, colon cancer is increasingly becoming a disease of the elderly with over 50% of the diagnoses occurring in patients over 70 years of age.

This thesis describes a cohort of patients diagnosed with colorectal cancer between 2002 and 2008 in the Zaans Medisch Centum, a teaching hospital in the vicinity of Amsterdam.

The first part of the thesis deals with patient related factors that influence prognosis and choice of treatment. The population included in randomised controlled trials investigating current treatment modalities does not correspond with the one seen in daily practice. The observational studies and sub-analyses of patients over 70 included in these RCT's do show a positive effect of surgery and adjuvant chemotherapy on survival. However, whether this means that those who choose conservative management are being under-treated remains the subject of further study.

Chapter one tries to quantify the influence of age and comorbidity on the outcomes of colorectal cancer. This retrospective cohort study shows that age and comorbidity influence survival despite the diagnosis of colon cancer. Furthermore, the percentage of patients dying from tumour related causes remains constant with increasing age/comorbidity while the number of patients dying from competing causes increases. This supports a choice for less intensive treatment for elderly frail patients as their expected survival benefit is reduced due to a reduced life expectancy.

Chapters two and three examine two subgroups of patients, the oldest of old, and the patients dying within 30 days of surgery. Increasing age and the extent of disease were primarily associated with perioperative mortality with almost half of the fatalities occurring after a palliative resection. Most frequent causes of death were abdominal sepsis and cardiovascular events. Of the octo- and nonagenarians 43% was still alive 5 years after the diagnosis. Of the patients dying within 5 years 32% died from non-tumour related causes, 22% due to complications of tumour treatment, and 46% as a result of the colorectal cancer. Clinicians should carefully weigh individual risk and benefit of treatment in frail elderly patients.

The second part of the thesis describes tumour and treatment related factors that are associated with risk of recurrence in the curative treatment of colorectal cancer.

Chapter four describes the association between dose reduction of adjuvant chemotherapy and risk of recurrence in patients with colon cancer. We found that a dose reduction of 5FU and oxaliplatin was associated with reduced recurrence free survival. Interestingly, reduction of just the oxaliplatin was not. Our study also adds to previous evidence that patients with high-risk stage 2 colon cancer should also be considered for adjuvant therapy.

Chapter five zooms in on the clinical importance of venous invasion in lymph node negative colon cancer and the risk of recurrence using a caldesmon stain to improve sensitivity for venous invasion. Our study strengthens previous evidence that venous invasion is an additional risk factor for recurrence comparable to the more accepted T4 stage of the tumour.

Chapters six and seven deal with neoadjuvant treatment for rectal cancer. Chapter six describes the outcomes of neoadjuvant radiotherapy. Survival was comparable in patients undergoing radiotherapy with a short or a long waiting period as well as patients not undergoing any neoadjuvant therapy. Patients not receiving radiotherapy had a lower disease stage, thus the hypothesis is that their expected survival benefit was offset by radiotherapy in the other groups. Interestingly, radiotherapy with a longer waiting period suggested a trend towards a lower disease stage in the resection specimen.

Chapter seven deals with the accuracy of MR in staging of rectal cancer. Patients undergoing surgery for rectal cancer with a pre-operative staging MR were included. We found a lower accuracy of the staging MRI for T-stage when compared to the resection specimen than reported in previous literature (61% vs. 75%). Thus, the accuracy of MR leaves much to be desired. Clinicians should be vigilant for under treatment based on the assurances of a low TN-stage on the MR. Radiotherapy led to significant down staging in the majority of patients. However, still 13% of patients showed a higher disease stage in the resection specimen.

In conclusion, this thesis is a major argument to include more patients over 70 years of age in prospective treatment trials for colorectal cancer. The elderly frail patient takes up an increasing part of daily practice with a lack of prospective randomised research in this population.

A less intensive treatment of this patient group can be considered based on increased risk of death from competing causes. However, overall survival of octogenarians undergoing curative surgery is reasonable, thus refraining from surgery should not be considered in general. Adjuvant chemotherapy can be omitted more easily as this deals with secondary prevention. Still, of the octo- and nonagenarians in our cohort, 22% of 5-year mortality can be lead back to a complication of tumour treatment. Staging of colorectal cancer and determining the appropriate treatment remains difficult despite major advances in imaging and risk stratification. High risk stage 2 colon cancer comes with recurrence risks similar to stage 3 disease and provides an indication for adjuvant chemotherapy. Especially the role of venous invasion as a risk of recurrence might be essential, sensitivity for this finding can be increased by using an elastic stain (which highlights the smooth muscle cells in the vascular wall). Neoadjuvant treatment regimens and staging through MRI remain subjects of debate. Clinicians should be aware of the limited accuracy of staging through MR. More sophisticated MR equipment may alleviate this problem in the future.

DISCUSSION

This thesis describes the treatment course of a cohort of patients diagnosed with colorectal cancer between 2002 and 2009 at the "Zaans Medisch Centrum", a teaching hospital near Amsterdam. In contrast to most populations this cohort provides a good representation of daily practice in the Netherlands. [1-3] The first part of the thesis deals with age and comorbidity and their effect on outcomes. The second part describes the added benefit of adjuvant chemotherapy in colon cancer patients. Specifically, the effect of dose reductions on recurrence free survival, and the role of venous invasion as a risk factor for recurrence in stage 1 and 2 colon cancer patients. The third part revolves around the pre-operative staging of rectal cancer through MRI and the most effective radiotherapy regimen.

Chapter one demonstrates that overall survival of patients with colon cancer is associated with comorbidity, as measured by the Charlson index, and age. However, this increased mortality cannot be attributed to death from colorectal cancer as the percentage of patients dying as a result of tumour progression/recurrence remains almost constant. We hypothesize that a less intensive treatment regimen in elderly patients is offset by an increased risk of death from non-cancer related causes. This hypothesis is strengthened in chapter four. Patients with stage 3 colon cancer receiving adjuvant chemotherapy are younger and have a lower Charlson comorbidity index than those receiving conservative therapy. They have an increased overall and recurrence free survival (OS 1.79 vs. 5.51 years p<0.001). However, the rate of recurrence (0.42 vs. 0.40 p=1.000) as well as the percentage of patients dying as a result of tumour progression is quite similar (40% vs 32% in favour of patients receiving chemotherapy).

Mortality in elderly patients with colorectal cancer remains high. In chapter 2 we report a 5-year survival of 43% in octo- and nonagenarians, 22% of mortality is attributable to treatment related adverse events. Two large cohort studies of octogenarians undergoing curative surgery for colon cancer report a 1-year overall survival of 78-82%. [4,5]

Considering the effect of dose intensity of adjuvant chemotherapy on recurrence free survival, the IDEA collaboration recently published the results of six randomised clinical trials in patients with stage 3 colon cancer receiving adjuvant chemotherapy comparing a 3-month FOLFOX or CAPOX regimen with the previously used 6 month regimen. [6] Noninferiority was established if the upper limit of the two-sided 95% confidence interval of the hazard ratio for recurrence after 3 years of follow up did not exceed 1.12. The meta-analysis of these trials did not manage to prove non-inferiority of the 3-month regimen with a hazard ratio for recurrence of 1.07 (95% confidence interval 1.00 – 1.15). In the subgroup analyses this increased risk of recurrence associated with a shorter treatment course appeared to pertain to those with a high risk tumour (T4 and/or N2 disease) with a HR for recurrence of 1.12 (95%CI 1.03 – 1.23). The 3-month regimen was non-inferior in patients without T4 or N2 stage disease (HR 1.01 (95% CI 0.9 – 1.12)). Notably, median age of the patients included in these trials was 64 and 79% of patients

had an ECOG performance score of 0, this does not correspond with daily practice in the Netherlands.

When examining the association of the relative dose intensity of chemotherapy with the risk of recurrence in our cohort, patients receiving a higher overall relative dose intensity of FOLFOX or CAPOX (5-fluorouracil and leucovorin or capecitabine combined with oxaliplatin) had an increased recurrence free survival (RFS 6.94 vs 5.11 years p=0.045). This finding disappeared when just examining the oxaliplatin relative dose intensity. The addition of oxaliplatin to fluoropyrimidines in patients over 70 has been subject to debate. Several meta-analyses have been performed pooling patients over 70 years of age from several clinical trials, as well as a number of cohort studies. To date, none of these show a convincing benefit of oxaliplatin added to a 6 month regimen. [7-11] Whether a 3 month regimen of capecitabine monotherapy might also safely be administered remains subject to further study.

In stage 2 colon cancer, the benefit of adjuvant chemotherapy is not as clear as in those with stage 3 disease. This is likely the result of the relatively good prognosis of patients with stage 2 disease with a 5 year recurrence free survival rate of 80% without adjuvant therapy. [12] However, in those patients with high risk stage 2 disease, such as a tumour invading the visceral peritoneum (T4 stage) or a poor tumour differentiation, the risk of recurrence is significantly higher and adjuvant chemotherapy may be warranted. We examined the role of extramural venous invasion (EMVI), as observed with a Caldesmon stain, as predictor of recurrence in patients with stage 2 disease. While our study was underpowered, a trend towards an increased risk of recurrence in tumours with EMVI was recognized. These findings are in line with the findings from previous studies. [13-15]

A recent update to the Dutch guidelines for the treatment of colorectal cancer simplified the criteria for high risk stage 2 disease to only include T4 tumours. This recommendation was based on 2 large cohort studies examining risk factors for recurrence in stage 2 disease. [16,17] However, in one of these studies the prevalence of venous invasion was unfortunately too low (3%) to determine its association with recurrence. In addition, the study bij Snaebjornsson et al. did show a number of other characteristics to be associated with cancer specific survival in patients with stage 2 disease including the number of resected lymph nodes (HR 0.50 for fewer than 12 nodes (95%CI 0.30–0.81)).

Considering the above, the current view on adjuvant treatment of colon cancer appears to simplistic. There are now 5 different treatment regimens available (not considering the difference between capecitabine and 5FU/LV): No chemotherapy, 6 months of fluoropyrimidine monotherapy, 6 months of oxaliplatin in addition to fluoropyrimidines, and 3 months of fluoropyrimidines with or without oxaliplatin (although the latter is yet to be studied). The results of the meta-analysis by the IDEA collaboration underline the importance of tailoring the adjuvant therapy based on the recurrence risk of the tumour in question.

This approach should integrate the various known risk factors for recurrence including but not limited to N-stage, T-stage, EMVI and number of resected lymph nodes. Furthermore,

patient age and comorbidity should also dictate the choice of therapy as a patients' life expectancy factors into the risk of recurrence as well as the expected survival benefit in quality adjusted life years (QALYs). Previous studies have tried to compare 2 or 3 different therapeutic options in subgroups of patients. However, if a model integrating several tumour and patient characteristics to guide therapy is to be created, a scoring system will have to be formulated and internally as well as externally validated. The addition of a physical performance assessment before starting treatment such as a "get up and go" test may prove invaluable as it is strongly associated with short-term morbidity and mortality after surgery. [18] Acquiring the patient data to construct such a model may prove challenging, especially since it will have to be based on observational data due to ethical constraints. Moreover, it will be essential to include a cohort of patients that includes the elderly and the frail to adequately reflect daily practice.

Patient characteristics will also greatly factor into the cost effectiveness of adjuvant chemotherapy. The median costs for a 6 month adjuvant treatment regimen with capecitabine are 5.229 euro, a regimen of CAPOX costs 14.783 euro, and a FOLFOX regimen costs 27.446 euro (the increased cost when compared to CAPOX can be attributed to the clinical admissions for infusion). Van Gils et al. found no significant differences in treatment costs when examining patients over and under 70. [19] There was a trend towards increased costs of therapy in patients with comorbidities. Using the outcomes of the MOSAIC trial as well as a Dutch observational cohort, the addition of oxaliplatin to a fluoropyrimidine netted a gain of 0.93 QALY with a cost of 11.854 euro per QALY. [20] Unfortunately, no cost-effectiveness evaluation has been performed for patients over 70 receiving combination therapy, but in the author's opinion its efficacy has yet to be proven. Regardless, with the expected changes to the duration of adjuvant therapy based on the IDEA collaboration outcomes, new analyses should be performed.

In chapter six and seven we confirm the outcomes of previous studies finding no difference between patients undergoing radiotherapy with a short or a long waiting period before surgery. [21,22] The accuracy of the pre-operative MR was also evaluated. Earlier reports describe a limited accuracy when assessing T-stage (72-75%) as well as N-stage (62-64%). [23,24] This is exemplified in our real world data where in 7 of 24 patients not receiving neoadjuvant therapy the pathologic T or N-stage was higher than estimated by MR. Nevertheless, the current treatment strategies based on pre-operative MR staging have been proven to be effective despite this inaccuracy. Conversely, the possibility of inter-observer differences in accuracy when evaluating staging MR's might result in inferior outcomes when they are not being assessed by dedicated experts. [25]

STRENGTHS AND WEAKNESSES

The main strength of this thesis is its population that is a good representation of the patients that present with colon cancer in the Netherlands in daily practice. Furthermore, all the patients had a follow up of at least 5 years and were subject to extensive chart review.

Thus there was more insight into comorbidity and causes of death than other studies which collected patients through large registries.

The main weakness of the thesis remains its retrospective nature and lack of randomization. Inherently, it is unable to demonstrate causality in the observed associations. Since the information gathered for this research was primarily collected to inform treatment decisions and document clinical decision making there were missing data. Some patient and treatment related factors were not regularly documented, including but not limited to physical performance, quality of life, and systematic tracking of treatment related adverse events. Also, patients were included between 2002 and 2008. In that period oxaliplatin was introduced to colorectal cancer therapy leading to heterogeneity in treatment. Treatment modalities have advanced even further since.

The relatively small sample size when compared to other observational studies leads to a lack of power to prove statistical significance. This in combination with the descriptive nature of the observational research makes it difficult to draw firm conclusions that lead to changes in standard daily care.

FUTURE DIRECTIONS

This thesis demonstrates patterns in patient outcomes that will hopefully increase understanding of the complex interplay of patient characteristics, treatment choices and outcomes. To improve upon this, it is imperative that investigators start including more elderly and frail patients in randomised trials for the treatment of colorectal cancer as reflected in the population seen in daily practice. Furthermore, the efficacy of adjuvant chemotherapy for colon cancer needs to be re-evaluated in a more robust model based on tumour as well as patient characteristics in order to determine the proper agents and duration of therapy for each patient. A more sophisticated algorithm accounting for the interactions between the various predictors will need to be created. However, the development of such a method will require detailed information for a large and diverse group of patients receiving a variety of different treatments. Collecting the data necessary to build such a model, and then validate it externally will prove challenging. Hopefully this will lead to individualized care not based on a clinician's intuition, but evidence based medicine.

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Addendum

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NEDERLANDSE SAMENVATTING

LIST OF PUBLICATIONS

LIST OF CO-AUTHOR AFFILIATIONS

DANKWOORD

NEDERLANDSE SAMENVATTING

Dikke darm kanker (colorectaal carcinoom) komt in Nederland steeds vaker voor met 15.427 nieuwe gevallen in 2016. Hiermee staat het binnen de oncologie bij mannen op de tweede en bij vrouwen op de derde plaats. Ondertussen neemt ook het percentage ouderen dat aan deze ziekte lijdt toe. Zo werd in 2016 67% van de nieuwe gevallen vastgesteld bij patienten van 65 jaar of ouder, 17% was zelfs boven de 80.

Er is in de afgelopen decennia veel onderzoek gedaan naar de behandeling van colorectaal carcinoom. Deze bestaat uit een operatie (als de ziekte niet is uitgezaaid) met daarbij in sommige gevallen chemotherapie en/of bestralingen. Er is met dit onderzoek grote vooruitgang geboekt waardoor het aantal recidieven is afgenomen en de levensverwachting van patienten toeneemt. Deze onderzoeken bestaan met name uit 'randomized clinical trials'. Hierbij krijgen deelnemers willekeurig een nieuwe behandeling of de gebruikelijke behandeling toebedeeld. Uit veiligheidsoverwegingen worden meestal verscheidene eisen gesteld aan de proefpersonen. Zo mogen ze geen andere ernstige ziektes hebben, moeten ze fit genoeg, en niet te oud zijn. Dit kan ertoe leiden dat de patienten die mee doen aan dergelijke onderzoeken geen goede afspiegeling vormen van de samenleving. Het is de vraag of oude en kwetsbare patienten dezelfde voordelen ervaren van de ingrijpende behandelingen die worden aangeboden voor de bestrijding van colorectaal carcinoom als met deze onderzoeken is aangetoond.

In dit proefschrift beschrijven we de patienten die tussen 2002 en 2009 behandeld zijn voor colorectaal carcinoom in het Zaans medisch centrum, een middelgroot streekziekenhuis ten noorden van Amsterdam. Het doel was om te kijken naar de resultaten van de behandelingen zoals deze in de landelijke richtlijnen worden geadviseerd in een doorsnee Nederlandse patientengroep. Hierbij wordt met name ingezoomed op de oudere patient en de patient met verscheidene bijkomende aandoeningen om te zien hoeveel baat deze heeft van behandeling, en waar deze uiteindelijk aan overlijdt: de darmkanker, de behandeling, of iets anders niet gerelateerds (zoals bijvoorbeeld een hartinfarct).

Het viel op dat oudere kwetsbare patienten minder vaak nabehandeld werden met chemotherapie dan hun jongere tegenhangers die dezelfde uitgebreidheid van ziekte hadden. Daarbij bleek dat de patienten bij wie door de behandelend arts was afgezien van chemotherapie minder lang leefden. Dit werd niet zozeer veroorzaakt doordat zij meer recidieven hadden, dit was procentueel ongeveer gelijk. Zij stierven vroeger en vaker aan andere ziektes of gevolgen van de behandeling. Desalniettemin was het aantal patienten ouder dan 80 dat kwam te overlijden als gevolg van de complicaties van een darmoperatie beperkt. Het is dus aan te bevelen deze groep bij kans op genezing wel te opereren tenzij de patient hele uitgesproken beperkingen of andere wensen heeft.

Tevens hebben wij gekeken of we aan de hand van de karakteristieken van de tumoren beter konden voorspellen of patienten een grote kans hadden op terugkeer van ziekte. Hierbij komen onze bevindingen globaal overeen met die van eerdere onderzoeken waarbij we zien dat invasie door de tumor van bloedvaten, de grote van de tumor, en

het aantal aangedane en onderzochte lymfeklieren belangrijke voorspellers zijn van een recidief en dat deze patienten dus eerder in aanmerking komen voor nabehandeling met chemotherapie. Wij pleiten voor een nauwkeurige afweging per patient waarbij zowel leeftijd en kwetsbaarheid, als deze tumoreigenschappen worden meegewogen in de besluitvorming ten aanzien van de behandeling. Om dit verder te verfijnen, en minder afhankelijk te zijn van de ervaring en intuitie van de behandelend arts, zal nog verder onderzoek nodig zijn. Hierbij is het essentieel om ook de oudere patient te includeren.

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LIST OF CO-AUTHOR AFFILIATIONS

R.J.L.F. Loffeld, department of gastroenterology, Zaans Medisch Centrum, Zaandam, Netherlands

S.D. Bakker, department of oncology, Zaans Medisch Centrum, Zaandam, Netherlands

M.J. Flens, department of pathology, Zaans Medisch Centrum, Zaandam, Netherlands

M.M.R. Mulder, department of pathology, Zaans Medisch Centrum, Zaandam, Netherlands

F.C. den Boer, department of surgery, Zaans Medisch Centrum, Zaandam, Netherlands

G. Fransen, department of radiology, Zaans Medisch Centrum, Zaandam, Netherlands

A. van Bochove, department of oncology, Zaans Medisch Centrum, Zaandam, Netherlands

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